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Liver cell transplantation for Crigler-Najjar syndrome type I: Update and perspectives

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Key words: Hepatocyte transplantation; Cell therapy; Inborn error of metabolism; Crigler-Najjar; Liver regeneration; Animal models

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INTRODUCTION
Crigler-Najjar (CN) syndrome is the paradigm of an inborn error of liver metabolism affecting the function of one enzyme, the 1A1 isoform of the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1)[4]. The parenchyma and thousands of other metabolic functions are normal, but the patient is at risk for severe neurological complications. Quality of life is deeply impaired, requiring phototherapy up to 12 h daily with efficacy lessening with ageing (probably due to unfavorable body surface/weight ratio and to increased skin thickness and pigmentation). Orthotopic liver transplantation (OLT) is a curative for the disorder[2, 3] but seems disproportionate to correct one single missing enzymatic function in an otherwise normal liver. Patients and physicians are often reluctant to undertake such an irreversible procedure and are seeking less invasive alternative options. Indeed, up to 15% of OLT patients require re-transplantation, and progressive fibrosis of the graft is a subject of concern at long term[6].

Auxiliary liver transplantation (ALT) is another curative approach that has the advantage of being reversible. However, ALT remains associated with major pitfalls. In addition to being an invasive surgical procedure, the technique is difficult mainly because of perilous anastomosis that can hamper the venous in- or outflow and can lead to graft atrophy/ischemia or vascular thrombosis. Another complication is the small-for-size liver syndrome, defined as liver impairment, following inadequate liver mass replacement[5]. The diagnosis of rejection is difficult because of minimal enzyme elevation.
Successful long-term results were recently obtained with gene therapy in Gunn rats\(^2\). This technique was described to depend on vector serotypes and allowed a reduction of serum bilirubin up to 64% after one year\(^6\). Globally, this technique is still facing with anti-UGT1A1 antibody production in the host organism, impeding the perpetuation of the metabolic effect\(^7\). Although encouraging, ex vivo gene transfer and cell injection is closely related to the quality of cell preparation\(^8\) and has not been documented in CN patients.

Other experimental protocols have been described, such as tin-mesoporphyrin treatment, for which feasibility has been demonstrated in two 17 year old patients\(^9\), or treatment with chimeric oligonucleotides that allowed a significant reduction of serum bilirubin in Gunn rats for up to 11 mg\(^10\).

Since the princeps report by Fox et al\(^1\), liver cell therapy (LCT) appeared as a new alternative treatment, which is intermediate between whole organ transplantation and gene therapy. Cells can be infused safely in the diseased liver, and are expected to bring sufficient enzyme activity to restore bilirubin metabolism, setting the patients within safer metabolic limits and improving quality of life. LCT has been shown to be able to restore metabolic function not only in CN patients\(^2\), but also in disorders of ammonium metabolism\(^11\), glucose metabolism\(^12\), clotting factor deficiencies\(^13\), and even complex enzyme systems such as Refsum disease\(^14\).

However, the technique remains insufficient; metabolic control is partial and durability of the result is limited to less than one year in most cases. Our aim is to review the current knowledge on the role of LCT to treat CN patients, report two additional patients, and review animal experiments performed as preclinical studies.

### LCT FOR CN DISEASE TYPE I

#### Lessons from the animal model

The Gunn rat model represents the rodent equivalent of CN disease and is characterized by a single mutation in the ugt1A1 gene. In this model, many experimental protocols using free or encapsulated liver cells have been designed with syngeneic/congeneic or allogeneic transplantation procedures\(^2\). Table 1 summarizes representative experiments. The best results were obtained when a hepatic injury was caused before LCT to create a niche and a regenerative stimulus for engrafting cells. The explanation for why the injury was beneficial is Gunn rats global liver function is normal, except for bilirubin conjugation, and the lack of host hepatocyte impairment fails to provide to donor cells a proliferative advantage. The repopulation rate necessary to observe a metabolic efficacy ranges from 5% to 10%\(^3\). Significant lowering of serum bilirubin could be observed up to 12 mo while using congeneric procedures\(^2\).

#### On the clinical side

Reports of human LCT for CN disease have shown encouraging results. The first demonstration of the efficacy of the technique was provided by Fox et al\(^1\). In this case, \(5 \times 10^9\) viable liver cells were infused in a 10-year-old patient and the effect was a significant decrease of bilirubin levels for up to 11 mo (Table 2). UGT1A1 enzyme activity was detected in the host liver and glucurononoconjugates were found in bile confirming...

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**Table 1** Representative liver cell transplantation experiments in the Gunn rat model

<table>
<thead>
<tr>
<th>Donor cells</th>
<th>Injection site</th>
<th>Hepatic injury</th>
<th>Outcome</th>
<th>Cell tracking</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 × 10^6 free or encapsulated congeneric Hc</td>
<td>Peritoneum</td>
<td>None</td>
<td>34.8% serum bilirubin reduction with encapsulated Hc vs 13.5% with free Hc at 1 mo</td>
<td>Light and electron microscopy</td>
<td>22</td>
</tr>
<tr>
<td>10 × 10^6 syngeneic Hc</td>
<td>Liver</td>
<td>Hepatectomy</td>
<td>Significant reduction of serum bilirubin up to 4 wk</td>
<td>ND</td>
<td>24</td>
</tr>
<tr>
<td>10 × 10^6 congeneric Hc</td>
<td>Spleen</td>
<td>None</td>
<td>Significant reduction of serum bilirubin up to 12 mo</td>
<td>ND</td>
<td>27</td>
</tr>
<tr>
<td>2-20 × 10^6 congeneric Hc</td>
<td>Portal vein</td>
<td>Right portal vein ligation</td>
<td>Significant reduction of serum bilirubin when injury with 2 × 10^6 Hc or with 20 × 10^6 without injury up to 30 d</td>
<td>UGT1A1 activity, WB, PCR for ugt1 gene</td>
<td>28</td>
</tr>
<tr>
<td>5 × 10^6 congeneric Hc</td>
<td>Spleen</td>
<td>Hepatic irradiation ± Hepatectomy</td>
<td>Normalization of serum bilirubin only with combined injury</td>
<td>UGT1A1 activity, WB, IHC</td>
<td>29</td>
</tr>
<tr>
<td>10 × 10^6 congeneric Hc</td>
<td>Spleen</td>
<td>Hepatic irradiation ± FasL-induced apoptosis</td>
<td>Normalization of serum bilirubin up to 160 d</td>
<td>UGT1A1 activity, WB, IHC</td>
<td>31</td>
</tr>
<tr>
<td>40 × 10^6 fetal or adult syngeneic Hc</td>
<td>Spleen</td>
<td>Retrorsine + Triiodothyronine</td>
<td>Significant reduction of serum bilirubin (+ conjugates in bile) up to 90 d (no difference between fetal and adult cells)</td>
<td>PCNA</td>
<td>32</td>
</tr>
</tbody>
</table>

Hc: Hepatocyte; IHC: Immunohistochemistry; PCNA: Proliferating cell nuclear antigen; WB: Western blot.
the integration of functional, healthy hepatocytes. Dhawan et al reported two additional patients ages 18 mo and 3 years, in which the reduction of serum bilirubin reached up to 50% and 30%, respectively over a follow-up period up of 7 mo (Table 2). Donor hepatocyte engraftment was illustrated by short tandem repeat analysis at 8 mo follow-up. Ambrosino et al also described a decrease of bilirubin levels up to 3 mo post-LCT, whereas they did not detect donor cells by using a short tandem repeat assay at 40 d follow-up [34].

We performed LCT in two CN pediatric cases (Table 3, Figure 1). The first patient was a 9 year old girl in whom a port-a-cath was placed in the jejunal vein. She received 18 cell infusions from three different donors over a period of 5 mo for a total of 4% of her estimated liver cell mass. Mean cell viability was high (80%) and no adverse events were noticed during the procedure. Pre-transplant serum bilirubin values attained 17.5 ± 0.49 mg/dL (mean ± SD) and dropped after LCT to the lowest value of 11.4 mg/dL (mean ± SD: 13.6 ± 0.42 mg/dL, P < 0.001). After a period of 6 mo, bilirubin values increased suddenly without a concomitant event and the patient was scheduled for OLT. For the second patient, the protocol was revised in order to provide a higher amount of cells within a shorter infusion period. She was 1 year old at the time

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Table 2  Summary of clinical liver cell transplantation procedures for liver-based inborn errors of metabolism

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Patient age</th>
<th>Cell amount (% liver cell mass)</th>
<th>Follow-up</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>5</td>
<td>7-41 yr</td>
<td></td>
<td>Partial reduction of LDL (3/5 patients)</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10 yr</td>
<td>7.5 × 10^9 (5%)</td>
<td>Donor hepatocytes detected by ISH at 4 mo</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decrease of bilirubin levels up to 11 mo</td>
<td></td>
</tr>
<tr>
<td>CN disease type I</td>
<td>1</td>
<td>9 yr</td>
<td>7.5 × 10^9 (5%)</td>
<td>Detection of UGT1A1 enzyme activity and of glucuronono-conjugates in bile</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>18 mo/3 yr</td>
<td>ND</td>
<td>50%-65% reduction of bilirubin up to 3 mo</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Donor hepatocytes not detected by short tandem repeat analysis at 40 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50%/30% reduction of serum bilirubin over 7 mo/ND follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Donor hepatocytes detected in one case by short tandem repeat analysis at 8 mo</td>
<td></td>
</tr>
<tr>
<td>Infantile refsum disease</td>
<td>1</td>
<td>4 yr</td>
<td>2 × 10^6 / 1 × 10^6 / 2 × 10^6 (4%/3%)</td>
<td>Donor Y-chromosomes detected by PCR at 7 d</td>
<td>20</td>
</tr>
<tr>
<td>Inherited coagulation factor II deficiency</td>
<td>2</td>
<td>3 mo/2 yr</td>
<td>2.2 × 10^6 (4%/3%)</td>
<td>Decrease in the factor II requirements</td>
<td>19</td>
</tr>
<tr>
<td>PFIC 2</td>
<td>2</td>
<td>ND</td>
<td>0.5 × 10^6</td>
<td>No improvement</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting tolerance: up to 7 h</td>
<td>18</td>
</tr>
<tr>
<td>Glycogen storage disease type I a</td>
<td>1</td>
<td>47 yr</td>
<td>2 × 10^6 (1%)</td>
<td>Increase of glycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improvement of diet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G6Pase activity detected</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improvement of ammonia levels</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Detection of enzyme activity</td>
<td></td>
</tr>
<tr>
<td>Urea cycle disease</td>
<td>1</td>
<td>5 yr</td>
<td>1 × 10^8</td>
<td>Transient metabolic improvement between 20 and 31 d of life</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0 d</td>
<td>10.5 × 10^8</td>
<td>Improvement of ammonia levels</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1 d</td>
<td>1.9 × 10^8</td>
<td>Increased urea synthesis</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>14 mo</td>
<td>2.4 × 10^5 (6%)</td>
<td>Improvement of psychomotor development and of ammonia levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.5 yr</td>
<td>4.7 × 10^9 (9%)</td>
<td>Urea neo-synthesis</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improvement of psychomotor development and of ammonia levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Donor hepatocytes detected by FISH at 12 mo and by enzyme activity at 8 mo</td>
<td></td>
</tr>
</tbody>
</table>

ASL: Arginino-succinate lyase; (F)ISH: (Fluorescent) in situ hybridization; LDL: Low density lipoproteins; ND: Not documented; OTC: Ornithine transcarbamylase; PCR: Polymerase chain reaction; PFIC: Progressive familial intrahepatic cholestasis.

Table 3  Presentation of LCT procedures in two Crigler-Najjar disease type I patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Infusion procedure</th>
<th>Timing of infusions</th>
<th>Donor cells</th>
<th>Cell amount</th>
<th>% Liver cell mass</th>
<th>Mean viability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 yr/Female</td>
<td>Porth-a-cath in jejunal vein</td>
<td>18 infusions/5 mo</td>
<td>Fresh and cryopreserved from 3 donors</td>
<td>6.1 billion</td>
<td>4%</td>
<td>80%</td>
</tr>
<tr>
<td>Patient</td>
<td>1 yr/Female</td>
<td>Broviac in portal vein</td>
<td>14 infusions/15 d</td>
<td>Fresh and cryopreserved from 1 donor</td>
<td>2.6 billion</td>
<td>8%</td>
<td>83%</td>
</tr>
</tbody>
</table>

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of the procedure and received 14 infusions from one single donor over 15 d to reach a total of 8.6% of her estimated liver cell mass. Cells were infused via a broviac catheter surgically inserted via a colonic vein to the spleno-mesentric confluent. Cell viability (mean 83%) and clinical tolerance were optimal. With pre-LCT levels of 17.6 ± 3.5 mg/dL (mean ± SD), the serum bilirubin dramatically decreased to values of 13.3 ± 2.4 mg/dL (mean ± SD) with the lowest value at 6 mg/dL. Skin jaundice reduced rapidly and the daily phototherapy schedule was alleviated from 10 to 8 h without any influence on the bilirubin levels. After 4 mo of progressive decrease of serum bilirubin, the values increased suddenly following an intercurrent Epstein-Barr virus (EBV) infection. The child underwent OLT without complications related to the previous LCT. Both patients received a methylprednisolone bolus and tacrolimus the day before and for 12 d after LCT. Subsequently they were given tacrolimus as long-term monotherapy.

**PERSPECTIVES**

At present, LCT remains limited by incomplete and time-limited metabolic control, mainly due to unfavorable immunological cell interactions, impaired donor cell quality and poor repopulation rates. Whereas the immunogenicity of liver cells is quite different compared to whole liver, the same immunosuppression protocols are applied for LCT and OLT. Additional fundamental in vitro studies are necessary for the development of the optimal immunosuppression protocol. In that way, Wu et al recently compared the effects of tacrolimus, rapamycin and mycophenolate mofetil on the engraftment and proliferation of engrafted liver cells in an allogeneic setting. They observed a deleterious effect of rapamycin on the proliferation of the transplanted cells. Serrano et al reported the lack of toxicity of tacrolimus and methylprednisolone on human hepatocytes in vitro. Other experimental protocols were designed to reduce the immunological pressure occurring in LCT procedures. For example, Mashalova et al obtained similar engraftment levels with syngeneic or allogeneic hepatocytes after their transduction with adenoviral early region 3 genes, suggesting a protective effect against rejection. This was related to the down-expression of Fas receptor at the cell surface leading to inhibition of Fas-mediated apoptosis. Protocols combining LCT with bone marrow transplantation with or without elimination of natural killer cells are being investigated. Liver cell encapsulation aiming to protect cells from the immune system has demonstrated promising results in Gunn rats. The technique is reversible and allows delivery of the cells to extrahepatic sites that are easy to access for sampling. However, major remaining hurdles are the creation of an adequate intracapsular microenvironment allowing long-term cell functionality and the restriction of this technique to an enzyme-delivery role. Host immunity can be modulated by co-transplantation of immunomodulatory cells, as developed by Le Blanc et al, using mesenchymal stem cells to control graft versus host disease in the bone marrow transplant setting. These cells and others, as non-parenchymal cells or liver-derived mesenchymal lineages, could provide permissive factors or a microenvironment allowing more favorable immunological cell interactions, although this has not been tested so far in LCT protocols. Study of inner mechanisms of cell rejection may also lead to improved clinical efficiency of LCT. For example, it has been shown recently that human hepatocytes exert a procoagulant activity depending on tissue factor expression, as previously demonstrated with pancreatic islet cells. In this work, Stéphenne et al demonstrated the improvement of the procoagulant activity by incubating the cells with N-acetylcysteine, making this drug valuable for additional in vitro studies.

Enhancement of liver cell engraftment capacity is another challenge. Engraftment depends on liver cell quality and host liver environment. While LCT is highly dependent on banking of cryopreserved cells, this procedure has been demonstrated to deteriorate cell quality. Indeed, although cryopreserved/thawed hepatocytes have been shown to possess in vitro clonal
replicative potential identical to freshly isolated cells\[^{52}\], their \textit{in vitro} potential seems to be restricted in time\[^{53-55}\] and their \textit{in vitro} functionality remains lower than that of freshly isolated hepatocytes\[^{56}\]. Furthermore, we recently demonstrated that, with the current protocols, cryopreservation/thawing of hepatocytes induces cell alteration and especially mitochondrial defects (complex I impairment)\[^{57}\]. Intracellular ice formation remains the major factor affecting the quality of cells. Protection delivered by non-permeating cryoprotectants must be further analyzed in terms of cell death and mitochondrial functions. New perspectives, such as vitrification, to avoid the crystalline state, coupled or not with encapsulation, must be validated in the future while considering the problem of hepatocyte de-differentiation at long term that could occur in this type of configuration.

Actions on the liver microenvironment have been evaluated in a recent report using monocrotaline, which is an alkaloid showing toxicity against liver endothelial and Kupffer cells\[^{58}\]. Authors reported an enhanced liver cell engraftment in a synergistic background mainly related to endothelial cell damage. Comparable studies were performed on dipeptidyl peptidase IV\[^{60}\] F344 rats using doxorubicin, irinotecan, or vincristine\[^{59}\]. In this study, Kim \textit{et al} showed improved cell engraftment after doxorubicin treatment attributed to endothelial cell disruption. While interesting, these approaches will not be applicable in a clinical setting. Physical alteration of the liver architecture was studied by Dagher \textit{et al} on nonhuman primates using partial portal vein ligation or embolization in an autologous LCT procedure\[^{60}\]. The authors reported hepatic regeneration rates up to 10% obtained at short term (15 d) after embolization of the portal vein. Others have successfully used chemicals as vascular endothelial growth factor delivered \textit{in situ}\[^{61}\] or by peripheral route\[^{62}\] to promote cell engraftment.

As stem cells were recently described to have a hepatocyte differentiation potential\[^{63,64}\], these are currently considered with growing interest for liver cell therapy. The most potent candidates are mesenchymal stem cells isolated from various tissues, with predilection for bone marrow,\[^{65}\] and umbilical cord\[^{66}\]. Liver progenitor cells\[^{67}\] or mesenchymal-like cells\[^{47,48}\] also deserve detailed attention. However, stem cells only display partial hepatocyte-like functionality\[^{64,68}\] and further advance is necessary to consider such cell types for therapy.

**CONCLUSION**

While LCT seems currently efficient and safe to improve the quality of life of CN diseased patients for a medium period of time, the technique still requires development to be considered for longer term or curative purposes. Advances must be focused on the quality of cell preparations together with the management of immunological barriers hampering reliable cell engraftment. Furthermore, other research areas, such as gene or stem cell therapy, are currently encountering exciting expansion, and combined therapeutic approaches would be justified in the near future.

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