

PERSPECTIVES

Clinical perspective on the use of human amniotic epithelial cells to treat congenital metabolic diseases with a focus on maple syrup urine disease

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Abstract

Congenital metabolic diseases are a group of hereditary disorders caused by the deficiency of a single specific enzyme activity. Without appropriate therapy, affected patients suffer severe neurologic disability and eventual death. The current mainstays of management attempt to slow disease progression, but are not curative. Several of these diseases have demonstrated significant benefits from liver transplantation; however, this approach is limited by the morbidity associated with this invasive procedure and a shortage of donor organs. Therefore, there is a need to establish a new strategy for improving the quality of a life for these patients. One potential solution is regenerative therapy using hepatocytes generated from stem cells. Herein, we discuss pertinent issues necessary for clinical application of the human amniotic epithelial cell, a type of placental stem cell. Focusing on maple syrup urine disease as an example, where liver replacement is an effective therapy, we explore this approach from a clinician's perspective.

KEYWORDS

cell transplantation, cellular therapy, liver regeneration, placenta, stem cell transplantation

1 | INTRODUCTION

Congenital metabolic diseases are a group of rare hereditary disorders caused by the deficiency of a single specific enzyme activity. Included in this group are organic acidurias, disorders of amino acid catabolism, urea cycle disorders, and lysosomal storage diseases. Most diseases of this class are autosomal recessive with identified causative genes. Left untreated, patients suffer multiple sequelae including intellectual disability, developmental delay, seizures, and eventual death. Although there is a low prevalence of each individual disorder, the number of overall patients has been increasing. The incidence rate of congenital metabolic diseases is estimated to be approximately 1 in 800 to 2500 individuals globally.¹⁻³

The mainstay of treatment is diet therapy. For example, patients with amino acid disorders need to take low protein medical meals free of the specific amino acid.⁴⁻⁷ Oral medications⁸⁻¹⁰ and enzyme replacement/substitution therapies have been attempted.^{11,12} However, none of these therapies are curative, and lifelong treatment is required. Currently, the only curative therapy for most of the congenital metabolic diseases is liver transplantation (LT). Although many successful cases of LT have been reported, this treatment carries significant disadvantages including the high morbidity associated with the invasive surgical procedure, and the need for lifelong immunosuppression.¹³ These limited treatment options represent a critical unmet medical need for these patients. To overcome some of these impediments, hepatocyte transplantation (HT) has emerged as an alternate to LT. Clinical studies have

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demonstrated that replacement of as little as 5% to 10% of the theoretical liver mass is sufficient to demonstrate a therapeutic benefit.¹⁴⁻¹⁶ Therefore, the less invasive cell replacement approach is suitable to treat congenital metabolic disorders; however, the limited source and quality of hepatocytes remains a problem.^{17,18} In search of an alternative cell source to human hepatocyte, regenerative therapy using stem cells has thus become a focus in order to develop treatment options.¹⁹⁻²²

Although embryonic stem cells and induced pluripotent stem cells carry this potential, applications are limited by: the associated ethical issues, the risk of tumorigenicity, immune mediated rejection of transplanted cells, and difficulties with cell expansion to a number needed to anticipate a therapeutic effect.²³ Among of the available stem cell types, human amniotic epithelial cells (hAECs) have attracted attention as an alternative to HT. hAECs are not encumbered by these issues with their unique properties including nontumorigenic, multipotency, immune privilege, and ability of immunomodulation.²⁴ In addition, several preclinical studies using murine models have demonstrated the therapeutic potential of hAECs for congenital metabolic diseases.²⁵⁻²⁷ A number of review papers focusing on these characteristics of hAEC have been published^{24,28,29}; however, there are no articles discussing the clinical use of hAEC transplantation from the clinicians' perspective. Herein, we discuss and explore the practical application of hAEC in the setting of a congenital metabolic disorder, maple syrup urine disease (MSUD: OMIM #248600), as the classical type of MSUD carries a high mortality rate without rapid intervention as will be described later, and LT is considered as a curative therapy.

2 | MAPLE SYRUP URINE DISEASE

MSUD is a metabolic disorder of amino acids caused by a deficiency in the activity of the branched-chain α -keto acid dehydrogenase (BCKDH) complex. This results in plasma accumulation of the branched-chain amino acids (BCAA): leucine, isoleucine, and valine. The corresponding branch-chain α -keto acids also increase in the urine, leading to the namesake odor.^{30,31} Dysfunction of any of the catalytic subunits of BCKDH including E1 α , E1 β , E2, and E3 can cause MSUD. The classical type of MSUD has less than 2% of normal BCKDH activity, whereas the intermediate type may have up to 30% of normal BCKDH activity.⁵ BCAAs, particularly leucine, play an important role in the maintenance of glutamate levels in the brain.³² As the CNS of neonates and infants are sensitive to leucinemia, neurological symptoms can develop, including irritability, poor feeding, lethargy, intermittent apnea opisthotonos, "bicycling" movement, and severe encephalopathy. Without prompt treatment, death is common.^{5,30,31}

Controlling plasma concentrations of BCAA while maintaining adequate caloric intake is essential for the medical management of MSUD. Patients must adhere to a special medical diet, which requires lifetime careful adjustments with BCAA-free formula along with supplementation of small amounts of natural protein.^{5,33} Even well-controlled classical MSUD patients cannot avoid periodic metabolic crises due to infection or starvation. Neonates and infants are at particularly high risk for decompensation, and once exposed to high leucine concentrations, irreversible CNS

Significance statement

This article discusses practical issues that might be raised when conducting a clinical trial of stem cell-based cell therapy for congenital metabolic disorders. In order to generate practical discussion on this topic, this review focused on maple syrup urine disease, for which there are limited treatment options. This is the first review from the perspective of clinicians who provide clinical care to the congenital metabolic disease patients. This review will help expedite the translation of a promising amniotic stem cell into clinical trials and elicit similar discussions pertaining to other stem cell types and diseases beyond congenital metabolic disorders.

damage can occur. Therefore, therapy must be initiated immediately upon diagnosis.³⁴

LT has been performed for classical MSUD and can restore 9% to 13% of whole-body BCKDH oxidation capacity.³⁵ Mazariegos et al reported the long-term follow-up in 37 patients who had undergone LT.³⁶ Patients and graft survival ratios were 100% with successfully corrected BCAA metabolism. These clinical data demonstrate the significant benefits of LT; however, the major complications which go along with this invasive procedure cannot be ignored.

HT avoids the morbidity associated with LT, and preclinical studies have shown cell replacement ratios up to 5% in rodent models³⁷ and up to 10% in a primate model.³⁸ The cell replacement ratio following clinical transplantation was evaluated in a case of argininosuccinate lyase deficiency. This patient received sex-mismatched HT, and at 12-month follow-up, the cell replacement and the enzyme restoration ratios were 12.5% and 2.6%, respectively.¹⁶ Other clinical studies have shown the therapeutic potential of HT for various congenital metabolic diseases including Crigler-Najjar syndrome type 1,³⁹ glycogen storage disease type 1,¹⁵ and urea cycle disorders.⁴⁰

The therapeutic benefit for MSUD has been also shown with a murine model of intermediate MSUD (iMSUD),^{41,42} whereas HT has never been attempted in MSUD patients. It must be noted that once the leucinemia-induced brain damage is established, it cannot be reversed. Thus, it is essential to treat the patients before the development of neurological injury. Although the less invasive HT may be suitable to treat patients in the earlier phase of the disease with comparable results to LT, the limited availability of primary human hepatocytes prohibits supplying the needed cells in a timely manner. Therefore, alternative cell sources must be identified to overcome this significant barrier.¹⁷

3 | PRECLINICAL AND CLINICAL STUDIES OF hAEC

Preclinical studies using murine models have revealed the therapeutic efficacy of hAEC for the treatment of several congenital metabolic

diseases including MSUD.²⁵⁻²⁷ Skvorak et al reported that hAEC transplantation improved survival and normalized the bodyweight of iMSUD mice. Treated iMSUD mice were euthanized at 100 days for analysis, whereas untreated iMSUD mice died within 28 days of birth. BCKDH activity doubled following hAEC transplantation and was maintained long-term in these immunocompetent iMSUD mice without signs of hAEC rejection.²⁶ One of the proposed mechanisms of this approach was that some of the transplanted hAECs differentiated into functional hepatocytes and expressed BCKDH enzymes, resulting in improved BCAA metabolism.

The safety of hAEC implantation has been clinically proven in young patients with Niemann-Pick disease type B treated by hAEC transplantation.⁴³ Despite repeated subcutaneous implantations, no signs of graft rejection or changes in lymphocyte subsets, including NK cells, were observed. Recently, in 2018, a first-in-human clinical trial of allogeneic hAEC infusion in premature infants with bronchopulmonary dysplasia was reported.⁴⁴ After the 2-year follow-up, no adverse events including tumor formation were observed.⁴⁵ Although these reports targeted the lungs via a different cell administration route, the results strongly support the safety of hAEC transplantation.

4 | CLINICAL APPLICATION

4.1 | Recipient criteria

In order to avoid the lifelong sequelae of acute metabolic decompensation, the ideal recipient for hAEC transplantation is an infant diagnosed with classical MSUD by newborn screening (Table 1). Those with the classical type of MSUD will likely demonstrate acute neurological symptoms in the neonatal period secondary to high leucine levels. hAEC transplantation might be beneficial in arresting symptom progression if performed immediately following recovery from this acute phase. This therapeutic approach might also benefit adult patients with uncontrolled intermediate MSUD (iMSUD), as repetitive episodes of metabolic crisis increase the risk of further clinical deterioration (Table 1).

TABLE 1 Criteria of recipients for hAEC therapy

Type of MSUD	BCKDH activity, % of normal	Plasma leucine concentration (μmol/L)		Episode of metabolic decompensation ^a	Notes
		At birth	Usual		
Classical	0-2	>760	Any	None or any	The patient's condition and the hemodynamics must be stabilized prior to the cell transplantation
Intermediate	3-30	<760	>380	More than once	The recipients will be patients who cannot control with diet therapy

Abbreviations: BCKDH, branched-chain α-keto acid dehydrogenase; hAEC, human amniotic epithelial cell; MSUD, maple syrup urine diseases.

^aEpisodes of medical care with neurological symptoms accompany with high leucinemia/ketosis including nausea, vomiting, anorexia, unconsciousness, and anxiety.

Although infants would most benefit from the hAEC transplantation, during the development stages of this cell therapy, adult iMSUD patients would be better candidates to confirm safety, cell doses, and delivery routes both because of the technical difficulty of cannulation in infants, and the potential ethical issues with introducing unproven therapies in neonates.

A major exclusion criterion for cell transplantation would be the presence of liver cirrhosis, as the presence of collateral circulation might increase the risk of cell embolism.⁴⁶ Additional exclusion criteria would include advanced cardiopulmonary disease, severe pulmonary hypertension, and active extra-hepatic malignancies.

4.2 | Patient recruitment

A well-designed randomized double blinded-controlled trial should be performed to provide evidence of therapeutic benefit; however, this would be difficult based on the small number of MSUD patients. Conducting a large-scale clinical trial would likely be impossible given the prevalence of MSUD is estimated to be only 1 in 185 000 infants worldwide.⁴ In addition, it is an ethical dilemma to conduct a randomized trial which requires a control group undergo a sham invasive procedure without anticipated benefit. Importantly, medical institutions that have established close and trusting relationships with the disease advocacy groups should take the lead in any such trial.

4.3 | Risks and benefits for recipients

Appropriate informed consent for any intervention includes a clear discussion of risks, benefits, and alternatives. Clinical trial consents tend to focus on potential benefits rather than risks, particularly for life-threatening diseases.⁴⁷ Even if a trial is burdensome and unlikely beneficial, some patients might prefer to receive it rather than waiting for deterioration. Therefore, when obtaining informed consent, clinicians need to be careful to avoid “therapeutic misestimation.” As iMSUD patients are often asymptomatic, they usually do not prefer to receive additional treatment if they can tolerate the strict diet therapy. It would

be unethical to mislead the iMSUD patients by overemphasizing the future risks of the disease. Particularly in the early phase of a clinical trial, it must be clarified that the patient bears potential risk with participation, and not guaranteed promise of therapeutic benefit.

Risks of hAEC transplantation include rejection of the cells, cell differentiation failure, post procedural infection, and bleeding from the liver parenchyma or puncture site. The potential for cell embolism should also be mentioned although it should be avoided by precise cell preparation. In cases of mild engraftment failure, increased risk would not be anticipated, as the procedure would not alter the patient's basal liver structure, and its baseline function would not be compromised. This would be one of the unique merits of hAEC transplantation in terms of the "opportunity cost," which should be discussed when designing clinical trials for cell therapy in general.⁴⁷ As the patients can continue with the basic diet therapy during this clinical trial, they would not have to forego the standard treatment while undergoing the clinical trial.

The proposed benefit of the cell transplantation is that the increased BCKDH enzyme activity following hAEC therapy could ease the restriction of protein intake, although the amount of protein a recipient could tolerate would depend on the basal BCKDH enzyme activity prior to the therapy. The procedure would be minimally invasive without laparotomy and would not carry the morbidity associated with orthotopic transplantation. As hAECs are readily available, in the future, patients could be treated immediately

without waiting for a deceased donor or incurring the risks for a living donor.

4.4 | Donor eligibility

Potential donors (birth mothers) would have to meet specific eligibility criteria. In the United States, the criteria are outlined by the US Department of Health and Human Services Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER) in Title 21 Code of Federal Regulations (21 CFR part 1271 Subpart C). The donors must be screened for "relevant communicable disease agents or diseases (RCDADs)." Furthermore, in order to avoid contamination by normal vaginal flora, donor placentas must be collected at the time of Caesarean section under sterile conditions.

Although the prevalence of MSUD is extremely low (1:185000), the possibility that a donor is the heterozygote cannot be ruled out. It has been reported that the enzyme activity of heterozygotes is about 50% of healthy donors.³⁵ Therefore, it would be ideal to exclude heterozygous donors by genetic screening prior to the cell transplantation. However, the current state of genetic analysis would not allow the detection of all of the asymptomatic inherited heterozygotes. Thus, routine genetic screening for donors would not be suitable as a standard pretransplantation evaluation.

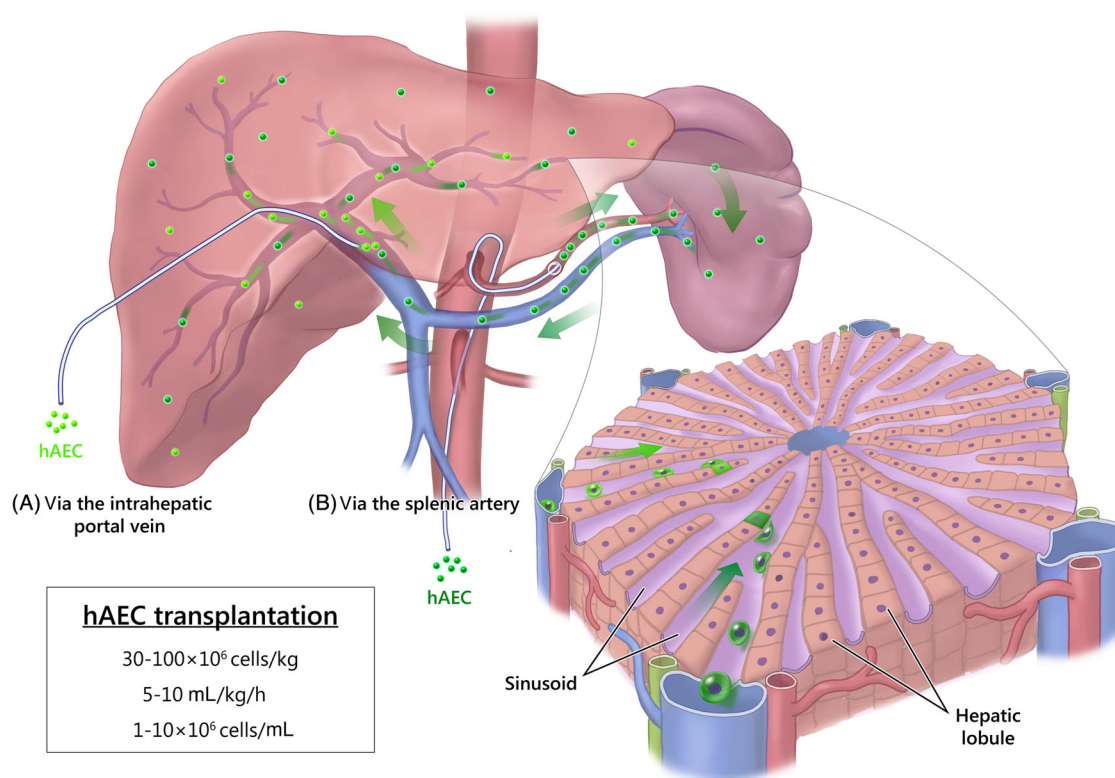


FIGURE 1 Clinical hAEC transplantation. The number of hAECs per infusion will be $30-100 \times 10^6$ cells/kg of body weight. There are two possible routes of hAEC transplantation: (A) transplantation through a portal catheter percutaneously and (B) transplantation into the splenic artery by the transfemoral approach. The infusion rate should be 5-10 mL/kg per hour, with a concentration of $1-10 \times 10^6$ hepatocytes/mL. The transplanted hAECs will be trapped in the peripheral portal vein and migrate into the liver tissue through the sinusoid. AO, aorta; CV, central vein; HA, hepatic artery; hAEC, human amniotic epithelial cell; Li, liver; PV, portal vein; Sp, spleen

4.5 | Practical considerations

The protocol for hAEC isolation has been described previously.⁴⁸ Cell characterization (identity and stability) and safety tests would be performed at a GMP-grade cell processing facility with FDA approved GMP-grade reagents in compliance with the requirements under 21 CFR part 1271.

Prior to hAEC transplantation, a general medical evaluation of the recipient would need to be performed, including whole amino and organic acid analysis, as well as a hepatic ultrasound and a portal venous system Doppler examination to identify the presence of cirrhosis or any other risk factors. Suspected infectious disease is an indication for postponement of the transplantation.

Other periprocedural considerations that could contribute to the overall safety of hAEC transplantation include mechanical ventilation, arterial line blood pressure/gas monitoring, and heparinization to minimize portal hypertension and hepatocyte thrombi formation. Cells could either be injected into the portal vein system via a percutaneously placed a portal catheter or into the splenic artery by the transfemoral approach (Figure 1). Based on current protocol for HT, we propose the following details: total number of hAECs per infusion would be $30\text{--}100 \times 10^6$ cells/kg of body weight, with an infusion rate of 5–10 mL/kg per hour, using a concentration of $1\text{--}10 \times 10^6$ cells/mL.¹⁴ Multiple hAEC injections might be required to stabilize the uncontrolled BCAA levels in treatment of adult patients. The optimal total cell dose could be determined for each case based on the patients' baseline BCKDH activity. Therapeutic efficacy would be evaluated using the measurement of the missing enzymatic activity (BCKDH) as well as monitoring correction of amino acid (BCAAs) levels.¹⁸ After allowing 7 days for engraftment and differentiation of the transplanted hAECs, natural protein intake could potentially be gradually increased if normalization of the serum leucine concentration had occurred. Following discharge, patients would need to follow a diet containing the predetermined amount of protein, with careful stepwise adjustment of leucine intake to maintain the concentration of leucine under 380 $\mu\text{mol/L}$. Regular follow-up of liver function, whole amino acid analysis, and hepatic imaging via ultrasound would be required to monitor the therapeutic efficacy of the transplanted hAECs. Once MSUD patients discontinue their diet therapy, it might become psychologically difficult to restart, so it would be better to refrain from a completely regular diet during this transitional period.

As hAECs exhibit both immune privilege and immunomodulatory properties, several studies attempted allogeneic hAEC implantation without immunosuppressants and showed the absence of an acute rejection reaction.^{43,44} However, there is no strong evidence of sufficient cell engraftment in the recipient tissue, and the mechanism of rejection in cell transplantation has not been fully elucidated. Therefore, like clinical HT, immunosuppressants would likely be required to improve cell engraftment at the first trial of allogeneic hAEC transplantation. The doses could potentially be tapered, and a biobank of hAECs might provide immunocompatible donor cells in the future.

5 | FUTURE PROSPECTIVE

Establishing a biobanking system based on the precise optimization using xeno-free cryopreservation media⁴⁹ would also potentially provide lifelong immunosuppression-free cell transplantation, which would enhance the value of hAEC therapy as affordable and effective treatment. Indications for hAEC transplantation would also likely expand if a therapeutic benefit was demonstrated. As many of the potential pitfalls have already been examined in clinical HT, standardized quality control evaluation protocols, cryogenic preservation, and infusion routes should follow the previous clinical cell transplantation studies.¹⁴

Preclinical studies^{26,27} showed the reproducibility of the therapeutic effects, and these as well as other congenital metabolic diseases should be explored as targets of this therapy. In the future, prenatally diagnosed metabolic diseases might be treated prior to phenotypic changes with in utero hAEC transplantation.⁵⁰ The immunomodulatory properties and antifibrotic effects of the human amniotic membrane might also alleviate liver fibrosis,⁵¹ which would expand the target pool of hAEC treatment.

In parallel with clinical translation, a number of questions must be answered. For example, the timing of cell engraftment and in vivo hepatic differentiation as well as the durability of the treatment need to be determined. As there is no suitable experimental model to study these questions without the influence of species differences, these answers could only be obtained through clinical trials.

6 | CONCLUSION

Cell replacement therapy is a promising approach to treat congenital metabolic disorders. In this perspective, we simulate a trial of hAEC transplantation to treat MSUD patients; however, we fully anticipate that this treatment strategy would be applicable for the treatment of other liver-based metabolic diseases. This perspective should help to design further studies toward clinical translation.

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CONFLICT OF INTEREST

Toshio Miki owns stock in Noveome Biotherapeutics, Inc. The other authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

C.T., T.M.: conception and design, financial support, manuscript writing; B.G., M.I., E.O., I.M., S.H.: conception and design, manuscript writing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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