Ethical and regulatory considerations of placental therapeutics

Abstract

Purpose: Placental therapeutics aim to treat placental disease. There are ethical and regulatory considerations if the drug also potentially affects the fetus. Drugs that might transfer or edit genes carry a specific challenge as currently fetal gene editing and fetal gene therapy are considered unethical.

Methods: This article reviews the literature on ethical and regulatory considerations for placental therapeutics.

Findings: Proposals for maternal gene therapy, directed to the maternal side of the placenta have been discussed with patients and stakeholders. No absolute ethical, legal or regulatory barriers to this potential treatment were identified. Patients who have experienced placental disease such as fetal growth restriction are keen for therapies; some would participate in first-in-human trials. Such trials need careful regulatory considerations such as the steps required to demonstrate safety and efficacy in pre-clinical models and the optimal animals for reproductive toxicology studies. *Ex vivo* dual human placenta perfusion experiments and villous explant *in vitro* studies allow drugs to be tested out in normal and diseased human placenta, providing short term safety and toxicology assessment. Testing drugs in non-human primates is an option but carries ethical and feasibility considerations. Selecting inclusion and exclusion criteria for clinical trial participants are important to ensure that the most suitable patients are exposed to a first-in-human drug. These will almost certainly be pregnant women with a high risk of perinatal loss and/or perinatal and maternal morbidity. Criteria should identify sufficient numbers of patients to make a trial feasible as well as a phenotype that will respond to the mechanism of action. How to dose

escalate and to capture information on adverse events are also key to optimal clinical trial design.

Implications: Developing placental therapeutics requires input from scientists, clinicians, regulators and close liaison with patients to ensure that new drugs are tested as safely as possible.

Keywords: adverse events, fetus, mother, ethics, gene therapy,

Introduction

Placental therapeutics aim to treat placental disease, such as placental insufficiency leading to fetal growth restriction or infection leading to preterm birth. Both conditions are major causes of perinatal loss and neonatal morbidity, with long term consequences for adult health. To date there is no treatment that can increase fetal growth *in utero,* or target deep-seated infection in the chorionic plate of the placenta. Novel ways to target drugs to the placenta are now in development. But there are a number of ethical, regulatory and trial design considerations that make clinical translation a challenge. This article reviews these barriers to innovation and signposts to some solutions in progress.

Ethical considerations

Developing therapeutics for placental diseases carries a variety of ethical considerations. There are major ethical concerns about drugs that might expose the fetus to genetic manipulation such as gene transfer or editing, although the debates are becoming more nuanced as genetic therapies come to clinic. In a systematic review on the public acceptability of gene therapy, the most common ethical concern was that genetic modification would interfere with nature or ''play God'' [1]. Generally however, treating a severe life-threatening disease was considered more morally acceptable compared with milder pathology or even non-therapeutic enhancement. The acceptability of germ line transgenesis was generally lower, with the potential for inadvertent germ line transmission to be of most ethical concern. Currently therefore placental therapeutics should try to reduce fetal exposure or even elude the fetus and certainly avoid altering the fetal germline.

Treating diseases during pregnancy involves two patients: the mother and the fetus, both of whom are impacted by the disease and the treatment. For clinical drug trials to be ethical, the therapeutic need for one patient must outweigh the risk imposed on the other patient. Placental therapeutics may benefit both the mother and fetus, for example treatment of chorioamnionitis or pre-eclampsia, which conditions can have life-threatening maternal and fetal impact. In other conditions such as early onset fetal growth restriction for example, the fetus may appear at first to be the only one with pathology, but cohort studies show that gestational hypertension commonly subsequently develops impacting the mother [2]. The risks of a drug treatment to the fetus however are very difficult to define, and may not appear until many years after birth. This is one reason for the exclusion of pregnant women from clinical trials. The adverse effects of diethylstilbestrol (DES), which was used to prevent early miscarriage during the 1940-70s, did not manifest until adolescence, with the finding of clear cell adenocarcinoma of the vagina and cervix in DES-exposed daughters and urogenital abnormalities in DES-exposed sons [3]. Epigenetic trans-generational effects may also need to be considered, as the intervention may potentially impact on the mother's future children via an effect on her eggs, and indeed that of a female fetus, whose eggs will be forming in the developing ovaries during gestation.

Ethical concerns about fetal therapy have been thoroughly discussed in the field of fetal surgery but are applicable to placental drug delivery as well. In fetal surgery, the decision to operate on the fetus *in utero* can be summarized as (i) pre-clinical animal studies indicate that the surgery is lifesaving or prevents irreversible damage to the fetus, (ii) the intervention reduces the risk of mortality and morbidity to the fetus compared to alternatives, and (iii) pre-clinical animal studies and theoretical risks indicate low risk to the pregnant woman, the current pregnancy, and future pregnancies [4]. Placental therapeutics

might be justifiable therefore when: there is reasonable certainty that the fetus will suffer irreversible and substantial harm without the intervention; the intervention is safe and effective; the risk to the health of the mother is negligible; and the mother can give informed consent to the intervention [5]. Evidence to support the answers to these questions will need to be provided on a case by case basis in order to support decision making for regulators, ethical review boards and parents about whether an intervention is ready for clinical trial.

A literature review on the ethics and legality of experimental treatments with advanced therapeutics for placental disease in pregnant women was conducted as part of the EVERREST project [6]. This is developing a clinical trial of maternal adenovirus VEGF gene therapy targeted to the uterine arteries and the placenta in women with early-onset FGR [7,8]. There were no ethical or legal objections to the proposed intervention or to a trial of this intervention, but two key questions were identified: 'is it ethical to give a pregnant woman a potentially risky treatment from which she does not benefit directly?' and 'is it ethical to treat a condition of the unborn child, who may then be born with a serious disability when, without treatment, they would have died?'. When these questions were discussed with stakeholders (disability groups, professional bodies and patient support groups) and women/couples who had experienced a pregnancy affected by early-onset FGR in semi-structured, qualitative interviews, the proposed clinical trial was viewed in positive terms. The risk of disability of the premature child was a concern, but women/couples were generally interested in participating in clinical trials that conferred a potential benefit to their unborn child, and they welcomed the development of new drugs for this untreatable disease.

There are also legal considerations for placental therapeutics that may be designed primarily to target the fetus that is unwell[9]. The legal position of fetal therapy varies hugely across the world with some jurisdictions such as the United States taking steps to protect the fetus legally, declaring its legal interest in fetal life, to others such as the United Kingdom where the law protects and enshrines maternal rights of autonomy over their bodies. There is the theoretical potential that a mother might be cajoled or even forced into treatment with a placental therapeutic for the health of her unborn fetus which would jeopardise her own rights. As fetal therapy advances therefore, legislators will be forced to reach a decision on the position of the fetus and the rights that it should be accorded.

Ethical considerations of paternal consent and the role of the father in the ongoing care of a neonate treated as a fetus are also important [10]. This is unlikely to be relevant to placental therapeutics where the target organ is disposed of after birth. However, if any interventions were to require ongoing postnatal application to the neonate after birth, and the child was unable to give consent, then parental consent would need to be reconfirmed after birth to allow ongoing participation of the neonate in any clinical trial.

Regulatory perspective

For many years, the development of new placental therapeutics has been hampered by industry underinvestment [11–14]. A review of a 2007 industry database found that only 17 drugs were under active development for maternal health indications. This was a fraction of the number for cardiovascular health (660 drugs) and fewer than for a single neglected disease such as amyotrophic lateral sclerosis (34 drugs)[15]. In the absence of industry Research & Development (R&D) investment in placental therapeutics, progress is relegated

6

to the less well-resourced efforts of publicly funded investigator-driven research. The strengthening of pharmaceutical regulatory procedures after the thalidomide and diethylstilboestrol teratogenic catastrophic events has made drug development far safer for all. But it is not surprising that the pharmaceutical industry has invested far less in development of new drugs for placental disease compared to other areas, where the safety hurdles are less significant and the duration of treatment longer than the time-limited use in pregnancy.

Over the last 10 years there has been a favourable new global health landscape in R&D to produce new drugs for neglected diseases. One potential way to address the underinvestment in placental therapeutics is to take advantage of orphan drug initiatives. Orphan drug legislation was originally introduced by the US Food and Drug Administration (FDA) in the United States in 1983 through the Orphan Drug Act to encourage the development of medicines for rare conditions that might otherwise be financially unviable [16]. The European Union (EU), Australia, Singapore, Japan, Taiwan and South Korea have since introduced their own legislation [17–19]. Application for orphan status is made by the sponsor, typically the company involved in the drug development, as it brings financial benefits such as access to scientific advice at a reduced cost and protection from market competition if the medicine is approved for use. To qualify for European Medicines Agency (EMA) orphan designation a medicine must meet the key conditions listed below [18],[19]:

 (1) The medicine is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; this is certainly the case for placental disease.

(2) No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to

those affected by the condition; this is very true for placental disease where no current treatments exist.

(3) The prevalence of the condition in the European Union is not more than 5 in 10 000 (FDA generally defines a rare disease or condition as affecting fewer than 200,000 persons in the United States) OR it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. These issues are further discussed below.

The short-term nature of pregnancy means there is little financial incentive to develop drugs for specific use in the gestational time window. Instead, safety and toxicology data in pregnancy are largely accumulated in post-marketing surveillance via off-label drug use in pregnancy. The time, cost, and design of Phase I, II, and III clinical trials will be huge especially as the safety bar for pregnancy therapeutics is likely to be even higher than for medicines development in all other populations. Innovative approaches to pricing medicines will therefore need to be established to recoup these costs, such as those already developed in the rare disease community whereby the most severely affected individuals are prioritised for intervention at first. When we consider pre-eclampsia alone, a 2012 study of US claims data found that the combined maternal and infant cost burden within a year of a pregnancy delivered before 28 weeks of gestational age was US$311,701 [20], with 91% of this cost related to treatment of the infant. An increase in gestational age at delivery by 2 weeks was estimated to reduce costs for all infants by US$1.15 billion annually. Therefore, small wins at extreme preterm gestations in terms of later delivery has a benefit in significantly reduced costs for obstetric disease.

The orphan designation process does not generally consider diseases split according to categories such as late or early onset; the disease is present or is not. This is a particular

problem for obstetric diseases which are considered to be syndromes, without very tight

diagnostic criteria such as genetic signatures, definitive histology etc. This may change with

progress in diagnostic blood markers but for the time being the diagnosis is usually made on

clinical grounds, such as significantly increased blood pressure and proteinuria, small fetal

size with abnormal fetal and maternal doppler blood flow, or cervical dilatation with regular

uterine contractions in the cases of pre-eclampsia, fetal growth restriction and preterm

labour respectively. Nevertheless, for all these pregnancy diseases, drugs have received

orphan designation. Almost certainly therapeutics will be first be tested out in those cases

at highest risk of maternal, fetal and/or neonatal morbidity/mortality from the disease.

Selecting the right cases in whom to first test out the therapeutics will be a challenge for

clinical triallists and is discussed later in this article. Further information on orphan

designation can be found from the FDA and EMA [21],[22].

Pre-eclampsia is listed on Orphanet as a rare disease [23]. Even though pre-eclampsia affects

between 3 and 8% of all pregnancies, in the context of the entire population, the number of

affected pregnant women is quite small, and has been estimated to be around 3.8 per

10,000, thereby comfortably achieving rare disease prevalence of less than 5 per 10,000

adult population. Pre-eclampsia achieved orphan designation in 2011 with the drug S-

nitrosoglutathione which was designated in both Europe and the US. Since then three other

drugs have also achieved orphan designation: digoxin immune Fab, recombinant human

alpha-1-microglobulin and recombinant placental growth factor (Table). Placental

insufficiency has also achieved orphan designation by the EMA [24]. The annual incidence of

placental insufficiency, defined as an estimated fetal weight below the 10th centile in the

presence of abnormal umbilical artery Doppler velocimetry, per 10,000 European Union

(EU) population was based on literature review and published national and EU statistics. The

proportion of affected pregnancies was estimated as 3.17% (95% CI 2.93% to 3.43%), using a weighted average of the results from two cohort studies [25],[26]. Using birth rates from 2012 and adjusting for a pregnancy loss rate of 1/100 gave an estimated annual incidence of 3.33 per 10,000 EU population (95% CI 3.07 to 3.60 per 10,000 EU population) which fell below the EMA threshold of 5 per 10,000 EU population.

The patient perspective

The potential for future parents to have an additional option when their fetus is diagnosed with a serious disease with prenatal onset, other than termination versus continuation of an affected pregnancy, is compelling. While determination of the risk:benefit ratio of placental interventions will entail assessment of multiple outcomes, it is recommended that safety be the primary outcome of initial clinical trials. In view of the potential risks of *in utero* therapy, it is essential that non-directive counselling is given, in which the options of no intervention versus the experimental intervention—with all possible risks and benefits—are explained without personal bias. This includes taking care with the language used to describe the clinical trial, such as using the terms "intervention" rather than "therapy". An independent healthcare professional or patient advocate to review patient understanding may be needed to ensure that the patient or couple are not under a "therapeutic misconception" but appreciate the experimental nature of the proposed intervention. The potential for life-threatening obstetric disease such as chorioamnionitis to be partially treated, resulting in survival of a neonate with an extremely poor quality of life, may be of great relevance to informed consent discussions.

Engaging with stakeholder and patient groups in the development and ongoing conduct of clinical trials of *in utero* therapy is useful. Patient groups can be key to disseminating

information about the option of *in utero* trials to potential participants. Patient groups have also provided input at a number of stages of protocol development for *in utero* stem cell transplantation clinical trials, including acceptability and ethical considerations of the proposed interventions, inclusion and exclusion criteria, participant monitoring and outcome measures [27],[28]. Patients recruited to an observational study of early-onset fetal growth restriction found the experience to be positive even when their pregnancy suffered a poor outcome such as a stillbirth [29]. The growth restriction, potential preterm birth and concern about their baby's survival heightened the women's need for information, but the ways in which information was initially and subsequently given about the growth restriction were key aspects of the women's experiences. The impact on trial participants of the need for frequent travel and organizing child care should not be underestimated. Some parents also described a threshold of "research fatigue" when asked about their or their baby's potential participation in other studies, as they wished to protect their baby, particularly if their child was preterm.

Demonstrating safety through pre-clinical and reproductive toxicology studies

A careful stepwise approach to treating the dysfunctional placenta is required when developing new drugs [30]. Proof of concept studies must be able to demonstrate drug/treatment efficacy *in vivo* on fetal and placental growth, maternal blood pressure, placental nutrient transfer and placental blood flow. Particular pregnant pre-clinical models can be used to answer specific aspects of the drug effect, for example growth restricted guinea pig models have a placenta most similar to the human for testing validity of concept [31]. Testing a drug in non-human primates is also an option and is often conducted for first-in-human (FIH) studies of large molecules. Pivotal toxicology studies to support the dosing regimen and duration for a first-in-pregnancy trial will be required and for them to be

conducted according to good laboratory practice (GLP). Use of pregnant non-human primates for toxicology of placental therapeutics carries ethical and feasibility considerations which require discussion with reproductive toxicology experts, but they may provide useful information if data on the safety of the drug outside pregnancy is limited. The dose range in toxicology studies should be broad enough to establish a no observed adverse effect level (NOAEL) with a sufficient margin of exposure over the maximum exposure proposed in a first-in-pregnancy clinical trial [32].

Supporting data may also be obtained from *ex vivo* dual human placenta perfusion experiments and villous explant *in vitro* studies which allow drugs to be tested out in the normal and diseased human placenta to provide short term measures of mechanism of action, safety and toxicology [33]. This technique is commonly used to test small drug molecules but has also been employed to determine the placental transport and potential pathological effect of gene therapy adenoviral vectors on the human placenta to support regulatory submission [34].

Conducting safe trials

Regulatory agencies are being presented with innovative trials of therapy in pregnancy to consider, particularly those of *in utero* therapy for genetic disease, two of which now have ethical and regulatory approval, one for osteogenesis imperfecta (www.boostb4.eu) [35] and a second for alpha thalassaemia major (https://fetus.ucsf.edu/node/406). A recent consensus statement from the International Fetal Transplantation and Immunology Society (IFeTIS, https://www.fetaltherapies.org) summarizes the experience of the panel of international experts who have brought these trials to clinic and considers how to enable safe testing of these novel therapies [36].

Safety evaluations must consider the risks of both the mode of administration and the product itself to the mother and fetus, and monitoring strategies aimed at detecting potential adverse events (AEs) need to capture both aspects. For all AEs, standard maternal and fetal criteria are defined in the Medical Dictionary of Regulatory Activities (MedDRA). The EVERREST Adverse Event Steering Group developed 12 maternal and 19 fetal new standard AE criteria which were adopted by MedDRA in 2016. Examples of new fetal AEs include fetal fluid collection, fetal tachyarrythmia, fetal movement disorder and abnormal fetal growth. It may seem obvious, but fetal AEs must be measurable *in utero*. Therefore, much of the fetal assessment will depend on imaging the fetus either via ultrasound or potentially magnetic resonance imaging, as well as cardiotocography and maternal subjective awareness of fetal movements.

Adverse events in pregnancy require specific considerations. For example, admission for routine maternal and fetal monitoring in the absence of pathology is common in pregnancy and should not be documented as an AE *per se*. In addition, AEs that have the potential to differentially affect the pregnant woman and the fetus such as vaginal bleeding for example, need to have separate maternal and fetal AE definitions and grading. A Delphi consensus led by this Group to grade maternal and fetal AEs has been completed and will be available shortly.

Neonatal adverse event criteria and grading are available via the Neonatal Adverse Events Severity Scale v1.0 developed in 2019 by the International Neonatal Consortium (INC) [37]. Neonatal AE severity was classified by five grades (mild, moderate, severe, life threatening or death) with severity defined by the effect of the AE on age appropriate behaviour, basal physiological functions and care changes in response to the AE.

Clinical trial design and dose escalation

Selecting the trial inclusion and exclusion criteria for clinical trial participants are important to ensure that the most suitable patients are exposed to a first-in-human drug. These will almost certainly be pregnant women with a high risk of perinatal loss and/or perinatal and maternal morbidity. Criteria need to identify sufficient numbers of patients and livebirths to make a trial feasible as well as a phenotype that will respond to the mechanism of action. In placental therapeutics this is challenging as obstetric diseases such as placental insufficiency and preterm birth for example mainly exist as syndromes rather than being defined by specific genetic or phenotypic diagnoses. Predictive tests are now becoming available to predict the need for delivery in women diagnosed with pre-eclampsia and threatened preterm labour [38],[39]. For early onset fetal growth restriction a multicenter cohort study is defining the clinical and biological characteristics of women from initial presentation to a fetal medicine unit through to two years of age [40]. These natural history studies are critical to designing appropriate inclusion and exclusion criteria for clinical trials of placental therapeutics as well as providing data on the types and frequency of AEs in the study population.

Monitoring AEs is central to assessing the safety of therapies and to capture information to allow safe dose escalation. For a first-in-pregnancy study, the primary outcome almost certainly will be safety, defined as the occurrence of Dose-Limiting Toxicity (DLT) events in the mother, fetus and neonate. The design of the EVERREST clinical trial has considered typical dose escalation methods used in oncology. These fall into one of two classifications: rule-based designs such as a 3+3 design with cohorts of three patients at prespecified dose levels, or model-based designs such as Continuous Reassessment Model (CRM) which may allow for more flexibility with faster acceleration to a potentially therapeutic dose [32]. The Maximum Tolerated Dose (MTD) will be the dose closest to a chosen target toxicity level

(TTL), defined according to the occurrence of DLTs. The DLT period therefore needs to be defined, starting at Drug Product administration and preferably within a short time point after birth so as to include information on maternal, fetal and neonatal AEs. The choice of the DLT period is important as if it is too long, for example up to 6 months of neonatal age, it will make the trial unfeasible to run due to excessive cost. Regulatory authorities may require sentinel dosing to further mitigate the risk in a first-in-pregnancy trial. This is typically used in FIH studies whereby subjects are dosed sequentially with an appropriate period of observation before the next participant is dosed. An example of a recruitment pattern for a clinical trial of a novel first-in-pregnancy placental therapeutic for early onset fetal growth restriction (FGR) is shown in **Figure 1**. The primary outcome of safety here is assessed two weeks after birth and a decision is made to dose escalate, de-escalate or remain on the same dose before treatment of the next patient can begin. Recruitment is shown as sequential, and on this basis it could take just over 3 years to complete 12 patients, illustrating the length of time that may be needed for first-in-pregnancy studies. If initial safety results were reassuring recruitment could become in parallel which would speed up completion.

Conclusions

There is a mismatch between the burden of disease for pregnant women and their infants on the one hand and investment in developing and testing pharmacological treatments on the other, and treatment of placental dysfunction is desperately needed. Designing therapeutics to target placental disease is challenging, but selected *in utero* therapies are now entering into a phase of collaborative clinical trials, paving the way for clinical translation of innovative drugs in pregnancy.

Table and Figure Legends

Table 1: Products receiving orphan drug designation in USA or Europe for the prevention or treatment of obstetric conditions. The EMA and FDA orphan designation websites were checked on 18th October 2020.

Figure 1: An example recruitment pattern for a clinical trial of a novel first-in-pregnancy placental therapeutic for early onset fetal growth restriction (FGR). The design assumes that the pregnant woman will be seen by the trial team at 21-22 weeks of gestation to confirm the diagnosis of early onset FGR and be approached about the trial. Two weeks are given to check trial eligibility criteria (for example exclude aneuploidy, virus infection and other causes of FGR), to confirm continued suboptimal fetal growth and dopplers and for the woman to decide on participation. At 23-24 weeks of gestation the woman is recruited and receives the trial intervention. Data from the EVERREST observational study suggests that the participant is likely to deliver around 28 or 29 weeks of gestation, up to 6 weeks after the trial intervention. Data on safety and Dose Limiting Toxicity (DLT) from the mother, fetus and neonate is available for the Trial Steering Committee to review two weeks after birth and to discuss with the Data Safety Monitoring Board on dose escalation. Assume it then takes another two weeks to set up the next patient for intervention, giving approximately 10 weeks between each patient. GA=gestational age of patient at intervention. DSMB=Data Safety Monitoring Board.

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