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COMMENT

Cell-based therapies in neonates: the emerging role of regulatory science

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The United States has among the highest rates of preterm birth of any developed country in the world. After a decade of decline, these rates have increased over the last three years despite more widespread screening of pregnant women for cervical shortening, avoiding elective delivery prior to 39 weeks gestation, and aggressive use of progesterone, cervical cerclage, and tocolytics to prolong pregnancy.[1] Evidence of chorioamnionitis is often observed in the placenta following preterm delivery, with the incidence increasing with decreasing gestational age.[2] The presence of chorioamnionitis may be a major contributor to preterm delivery and the subsequent development of sepsis, white matter injury (WMI), and bronchopulmonary dysplasia (BPD) in preterm neonates.[3]

Despite increased legislative efforts in the United States and abroad to promote the development of important therapeutic agents (e.g., drugs, biologics, devices) for preterm neonates, there are currently no treatments available to prevent these serious complications. These efforts include the passage of the Orphan Drug Act which grants special status to a drug or biologic to treat a rare disease (common in preterm neonates). (https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/ucm364750.htm) In fact, there have been few treatments developed specifically for preterm neonates that have significantly improved survival and outcome in the past 20 years. It is clear that innovative approaches to improve outcome in this high risk population are urgently needed.

In this issue of Pediatric Research, Paton and colleagues administered a daily dose of lipopolysaccharide (LPS) or placebo intravenously for three consecutive days to chronically instrumented fetal sheep at 0.65 gestation.[4] This was followed by a single intravenous dose of either allogeneic umbilical cord blood (UCB) cells or mesenchymal stem cells (MSC). While LPS was associated with significant neuroinflammation and apoptosis, UCB cells and MSCs reduced astrogliosis and cerebral apoptosis and protected mature myelinating oligodendrocytes. A finding of particular interest was that the two cell types had different neuroprotective effects within the brain, suggesting separate mechanisms of action. The ability of these cells to mitigate neurologic injury in the fetus was compelling and suggests a potential role for cell-based therapies in the prevention of neurologic injury and improved neurodevelopmental outcome in preterm neonates. It is not clear how these treatments might potentially be administered in human trials; would they be given directly to the "high risk" fetus (the development of chorioamnionitis usually results in expedited delivery) or would they be equally effective when given to a preterm neonate immediately after delivery. Clearly, a more comprehensive analysis of the safety and efficacy of these products in preventing neurologic injury in preterm pre-clinical models is needed before clinical trials can be initiated in preterm neonates. However, early studies examining the role of biologics to prevent complications of prematurity are already underway. In one recent study, preterm neonates received a single intratracheal dose of MSC's (in a dose escalation fashion) to examine safety, with the ultimate goal of attenuating the incidence and severity of BPD in a larger multisite, randomized, controlled study (ClinicalTrials.gov:NCT01828957).[5]

When developing a drug or biologic to prevent a rare condition such as WMI or BPD, an adequate understanding of the population, the disease's natural history, the pathophysiology of the disease, and the drug/biologic's mechanism of action is needed. Non-clinical toxicology and human toxicology (from multiple organs and tissues) must also be available to support the proposed clinical investigation(s). Most importantly, identifying clinically relevant, validated, age-appropriate, condition-specific efficacy and safety endpoints is essential. While Paton et al were able to examine the brain of these preterm lambs, other indirect measures will be needed for preterm neonates such as magnetic resonance imaging (MRI) or cellular/biochemical biomarkers such as cerebral spinal fluid IL-1β concentrations.[4] The development and qualification of these biomarkers (e.g., enrichment, predictive) will be needed to facilitate the conduct of clinical trials using these biologics. (https://ncats.nih.gov/enews/issues/vol05-iss05/best-biomarker-glossary) Ultimately it will be important to demonstrate improvement in neurodevelopmental outcome with the Bayley III or other standardized and validated assessment tools at 2 years of age and later in childhood when language and behavior can be better evaluated.

There are significant differences between drug development and the development of biologics for preterm neonates, especially with respect to manufacturing processes. The Center for Biologic Evaluation and Research (CBER) and not the Center for Drug Evaluation and Research (CDER), is the Center within the Food and Drug Administration (FDA) that regulates the use of biologics in humans. (https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/) CBER is responsible for working with investigators and sponsors to address the additional hurdles in developing targeted therapies (e.g., UCB cells and MSCs) for a high risk population such as preterm neonates. These cells are complex mixtures and derived from living sources. They are heat sensitive and susceptible to

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contamination from outside sources, with strict aseptic principles needed during the manufacturing process. The research conducted with these cell types often involves a variety of medical conditions that usually have few readily available treatments and are targeted to small populations. This is especially true for preterm neonates where over 90% of the drugs and biologics used in their treatment are not approved for their intended use by the FDA. This means that sufficient safety and efficacy studies have not been conducted in neonates to support their use. In addition, there are relatively few drugs and biologics currently in the "development pipeline" designed specifically for the prevention and/or treatment of preterm neonates, making the development of innovative biologics to prevent important complications particularly important.

There are several pathways that exist at FDA to expedite the development of high profile treatments such as cell-based therapies. However, multiple criteria must be met to qualify including:

1. Treating a serious or life-threatening condition
2. Addressing an unmet medical need
3. Better and potentially safer than any other available therapies
4. Preliminary non-clinical and/or clinical evidence suggesting the possibility of substantial improvement of a clinically meaningful endpoint
5. Surrogate endpoints likely to predict clinical benefit

Additional challenges exist with testing and characterizing cell-based therapies in preterm neonates that Paton et al and other investigators working in the field must consider in order to translate these important pre-clinical findings into viable treatments for the fetus and/or neonate. First, significant patient-to-patient variability exists and not every fetus exposed to chorioamnionitis *in utero* will develop WMI and subsequent cerebral palsy. Determining which fetus and/or preterm neonate is at highest risk (e.g., enriching the population) is critical in order to target the therapy and maximize the potential benefits, while limiting any risk. Next, there is significant cellular heterogeneity and multiple potential mechanisms of action with different cell types as demonstrated by Paton et al.[4] Difficulty in controlling variability, inability to sterilize the products, and the use of small lot sizes (with limited material) may also pose additional burdens on investigators. Finally, keeping cells viable for prolonged periods of time prior to administration and the lack of appropriate reference standards may be particularly problematic.

It is imperative that investigators and sponsors interact at the earliest stage of product development with the FDA and other regulatory agencies in order to harmonize approaches to obtain high-quality pre-clinical and clinical safety and efficacy data. Developing adequate safety profiles for biologics in preterm neonates can be complex due to the highly variable rate of background complications in this population which is challenging for regulators, Institutional Review Boards, and Data Safety Monitoring Boards. Optimal approaches to better defining safety and efficacy for neonatal clinical trials are clearly necessary.

To facilitate these efforts, collaborations within the neonatal community to add clarity, rigor, and predictability during the development of medicinal products for neonates are currently underway. The International Neonatal Consortium (INC) was established by a grant from the FDA to the Critical Path Institute and is a public-private partnership that engages multiple global stakeholders to promote clinical drug development for neonates.[6] Operating in the pre-competitive space, INC addresses the need for measurement and assessment of clinical outcomes in neonates through teams that share data and expertize to advance regulatory science. Two other new networks have been established to facilitate multisite, multinational clinical trials in Europe (The Connect 4 Children Consortium, C4C) and in the US (Institute for Advanced Clinical Trials for Children, IACT).[7,8] These networks are highly promising initiatives to increase the efficiency of conducting pediatric drug, biologic, and device trials in multiple countries simultaneously while providing significant expertize to streamline all aspects of the clinical trial process. The most important factor remains selecting clinically meaningful endpoints (both short and long-term) that will be acceptable to regulators, investigators, and families.

It is critically important that we bring effective new therapies to neonates as quickly as possible. Improvements in speed and efficiency will require engaging key stakeholders in multiple countries simultaneously. While Paton and colleagues have demonstrated that cell-based therapies appear to hold great promise for the prevention and/or treatment of a variety of serious neonatal disorders,[4] there are significant challenges that these investigators will need to overcome prior to widespread use. The academic community, regulators, funding organizations, industry, and nursing and parent groups must work together to help make this vision a reality.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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