


ADVANTAGES AND PERILS OF CLINICAL TRIALS

Exploring new therapies for children with autism: “Do no harm” does not mean do not try

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Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that are mainly characterized by deficits in social communication and interactions. Repetitive behaviors and/or interests and sensory sensitivities are also common. Many individuals also have comorbidities, including intellectual disability, adaptive skill deficits, anxiety, and aggressive behaviors. The prevalence of ASD is reported to be 1:68 (Centers for Disease Control and Prevention, 2016) with boys affected at a higher rate than girls (4.5:1).

ASDs are present in children from a very young age and with modern diagnostics can be diagnosed by <24 months of age. While autism is not a fatal disease, it causes lifelong morbidity in many affected individuals and their families. Those diagnosed with ASD who also have intellectual disability are unlikely to be able to live independently and may be dependent on parental/societal care for their entire life. There are currently no approved therapies that address the core symptoms of autism. Thus, there is a keen interest in exploring novel therapeutic approaches to the condition.

ASDs are a heterogeneous group of disorders, and it is likely that the etiology of disease is not the same in all cases. Broadly, there is evidence that genetic mutations may be responsible for the disorder in <10% of cases. There also is evidence that neuroinflammation, either in utero or postnatally, may play a role. Furthermore, as named, ASD is a spectrum of disorders that vary in severity, impact on the individual and their family, and selection of and efficacy of interventions and treatments.

Cellular-based therapy is undergoing testing in clinical trials for many neurological diseases including, but not limited to, cerebral palsy, hypoxic ischemic encephalopathy, severe traumatic brain injury, spinal cord injury, stroke, and ASD.¹⁻³ Mesenchymal stromal cells (MSCs) derived from bone marrow or cord or other

birthing tissues, cord blood cells, and bone marrow cells are all undergoing testing in early phase clinical trials. In most studies, cells are delivered intravenously, but in a few, cells are given intrathecally. There are claims identifying modulation of neuroinflammation as the mechanism of action of these various cells, but none are fully substantiated at this time. In addition to formal clinical trials, there are many unproven stem cell interventions, offered without regulatory oversight by clinics with varying qualifications, which are available on a fee-for-service (also known as “pay to participate”) basis that can be classified as “medical tourism,” risky, and/or unproven treatments.

The identification and use of objective and validated outcome measures in clinical trials in children with ASD is very challenging. Measures generally involve, at least in part, parent-reported behavioral outcomes that are difficult to administer and standardize. It is critical before claiming a benefit of a particular intervention, to conduct one or more phase III randomized, blinded, placebo-controlled clinical trial(s) to confirm true responses and to differentiate placebo/expectancy effects from true responses. In addition, studies in children, who are developing, growing physically, and changing, are more difficult because of the need to differentiate a change from expected development to an effect of the intervention undergoing testing. Of note, to date there have not been any therapeutic interventions that have demonstrated efficacy in formal phase III clinical trials in children with ASD.

Over the past few years, SCTM has published eight manuscripts reporting results of small early phase clinical trials of cord blood (n = 4), induced pluripotent stem cells (n = 1), cord tissue MSCs (n = 2), or bone marrow cells (n = 1) in children with ASD. Highlights of some of these studies are described here.

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Dawson and colleagues conducted a phase I, open-label study, determining that autologous cord blood infusions were safe and feasible.⁴ The authors hypothesized that the treatment reduced symptoms in children with ASD because cord blood cells modulate inflammatory processes in the brain. Twenty-five children, aged 2-5 years (median age 4.6), were enrolled. Patients had to have stored a qualified banked autologous cord blood unit. There were no serious adverse events related to infusion. Improvements in parent-reported outcomes of social communication skills improved in children with a nonverbal IQ >70 in the first 6 months post-treatment. Assessments using the Vineland Adaptive Behavior Scales-II (VABS-II), a caregiver questionnaire that assesses socialization, communication, daily living skills, and motor skills, showed a significant improvement in the socialization and adaptive behavior domains, but not in the communication domains, in the first 6 months after treatment. There was no further improvement from 6 to 12 months. Eye tracking and electroencephalogram (EEG) results correlated with the responses seen on the VABS-II.

Another cord blood study used a randomized, placebo-controlled, crossover design.⁵ Twenty-nine children with ASD, aged 2-6 years, were enrolled. Patients received autologous cord blood or placebo, were evaluated at 12 and 24 weeks, and then crossed over to the opposite treatment. There were no serious adverse events. Multiple endpoints were evaluated, and although there were trends toward improvement on the VABS and other socialization scales, there were no statistically significant differences for any endpoints.

A phase II randomized, placebo-controlled, double-blind clinical trial was recently published in the *Journal of Pediatrics*; 180 children with ASD, aged 2-7 years, were randomized to either autologous (n = 56) or unrelated donor partially HLA-matched allogeneic (n = 63) vs placebo (n = 61).⁶ The study was modeled to enroll a minimum of 143 children with a nonverbal IQ >70 to be powered to answer the primary study question, but due to a flaw in study design, only 101 of the 280 enrolled children met this criteria. Nonetheless, the study was analyzed as enrolled. The cord blood infusions were well tolerated. Analysis of the entire cohort showed no evidence for improvement in the primary endpoint, which was the VABS-III Socialization Domain in the treatment arms. A large expectancy effect was observed in the placebo arm in many of the behavior measures. A subset analysis of children without intellectual disability, the intended study population, showed significant improvements in the VABS Communication Domain, eye-tracking, EEG, and the Clinical Global Impression-Improvement scale in children treated with cord blood.

In another small, open-labeled study, allogeneic MSCs derived from umbilical cord tissue were administered to 20 children with ASD.⁷ Efficacy was evaluated with the Autism Treatment Evaluation Checklist (ATEC) and the Childhood Autism Rating Scale (CARS). Patients received four intravenous treatments over a 9 month period, and were followed at 3 and 12 months. There were no serious adverse events. Both the CARS and ATEC scores of eight subjects decreased over the course of treatment, placing these children in a lower ASD symptom category when compared with baseline. Inflammatory cytokine levels also decreased. In this report, the benefit was mild, but hypothesis generating for future investigation.

Significance statement

Autism spectrum disorders are a significant cause of morbidity. Cellular-based therapy is one evolving option for this disease. This article reviews the data to date and strategies for the future.

Earlier this year, the Duke group published their experience with 12 children with ASD, aged 2 to 11 years, treated on an open-label phase I study investigating MSCs derived from allogeneic cord tissue MSCs.⁸ Children were treated with 1, 2, or 3 infusions of 2×10^6 cells/kg separated by 2 months each. All of the infusions were well tolerated. Low titer, anti-class I HLA antibodies targeted against HLA loci on the MSC donor cells and not on the patients' cells, developed in half of patients. Fifty-eight percent of the patients showed improvement in two of three behavior endpoints that were described in the results. The authors concluded that infusions of cord tissue MSC are safe and that further randomized studies are needed to determine efficacy.

The study by Thanh et al.,⁹ "Outcomes of bone marrow mononuclear cell transplantation combined with interventional education for autism spectrum disorder," published in a recent edition of the journal has stimulated conversations and controversy. The article described an early phase open-label, nonrandomized study of intrathecal autologous bone marrow mononuclear cells combined with educational intervention for children with ASD. The authors inaccurately described the therapy as "transplantation," which was misleading. The therapy was comprised of two intrathecal doses of bone marrow cells, one at baseline followed by 8 weeks of behavioral therapy and a second repeated 6 months later. The primary outcome measure was the CARS score. The authors reported improvements in multiple behavioral endpoints within 18 months of treatment and concluded that the therapy was safe and that further randomized placebo-controlled studies are needed.

In response to this paper, Dr. Heather Finlay-Morreale wrote a passionate letter to the editor questioning the ethics of performing this trial in children with ASD.¹⁰ Specific criticisms included the fact that the risk of toxicity of the intrathecal route of administration of cells was not justified, particularly in vulnerable children who could not consent for themselves. In response to Dr. Finlay-Morreale's letter, the authors of the manuscript wrote a rebuttal, which is published in this issue of the journal. In addition, the journal's editorial staff felt compelled to address her concerns in a broader sense. Some children with autism can have mild deviations from neurotypical behaviors with normal intelligence and can navigate their world with accommodations from others. More often, though, children with more severe manifestations of autism, especially with comorbidities that cause intellectual disabilities, cannot navigate their world and create seemingly insurmountable challenges for their families, siblings, teachers, therapists, and others. Frankly, there are no therapies that effectively modify the core symptoms of autism and new treatments are needed. Thus, the justification of the need for effective and safe interventions is evident.

Dr. Finlay-Morreale makes some valid points in her letter, particularly that Thanh and colleagues did not treat the children in their series with stem cells. Bone marrow-derived mononuclear cells were used. In addition, the cells were not transplanted; rather they were administered via intrathecal injection with no preparative therapy or intent of engraftment. As both authors of this position piece are experienced in administering intrathecal chemotherapy in patients with hematological malignancies and Dr. Kurtzberg also has limited experience giving cell therapy intrathecally to children with leukodystrophies, we do not agree that performing spinal taps on children will result in “lifelong pain or bleeding into the spinal cord causing paralysis.” Having said this, we do agree that intrathecal administration of cells would have likely undergone additional scrutiny in the United States before it could be incorporated into a clinical trial in children with ASD. Furthermore, the manufacturing of the cells and final formulation for administration could significantly increase (or decrease) the safety of the intrathecal dose. Specifically, red blood cells should be eliminated from an intrathecal formulation. Furthermore, only certain solutions are safe for intrathecal administration (Ringer's lactate, Elliot's B solution) and the authors did not specify these details about their cellular product.

At SCTM, we feel that it is important to publish manuscripts describing early phase clinical trials in this new and emerging area. The early studies will not be perfect, but with transparent and constructive discussion among the stakeholders, in peer-reviewed medical journals—not through social networks or blogs—accurate information will be disseminated and subsequent studies will be improved. These scientific publications will also be vetted by review teams and critiqued in a way that improves the overall quality of their manuscripts. This practice should also encourage the “bad actors” to present their results in a legitimate scientific journal rather than in the lay press or through testimonials or on blogs. The scientific community, parents, and medical professionals caring for children with autism need to work together to better understand the various forms and etiologies of this heterogeneous disease, to identify the children who are in need of therapy, and to evaluate the safety of various approaches. We look forward to learning about more advances in this complex disease.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

K.B., J.K.: contributed to the design, research, writing, and review of this manuscript.

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