CORRESPONDENCE

Risdiplam for Prenatal Therapy of Spinal Muscular Atrophy

TO THE EDITOR: Risdiplam, a small-molecule drug that modulates splicing of the gene *SMN2*, increases the level of the protein SMN (survival motor neuron) in persons with spinal muscular atrophy (SMA) and ameliorates disease manifestations.[1,2] A fetus at risk for the severe form of SMA — type 1 SMA — owing to having a deceased older sibling with genetically confirmed type 1 SMA, was tested for SMA by means of amniocentesis. Testing showed no copies of *SMN1* (confirming the diagnosis of SMA) and two copies of *SMN2* (which is predictive of type 1 SMA).[3] Previous data have shown transplacental passage of risdiplam-related material and supported the feasibility of prenatal treatment.[4] We report here the treatment of this fetus with risdiplam.

The Food and Drug Administration and the local institutional review board approved the single-patient investigational plan. The parents provided written informed consent in consultation with an unaffiliated advocate. F. Hoffmann–La Roche provided scientific advice, advised on the safety of prenatal exposure, and supplied risdiplam at no cost as an investigational product under a confidentiality agreement with the sponsor (St. Jude Children's Research Hospital).

Risdiplam was administered orally to the mother at a dose of 5 mg per day between 32 weeks 5 days' gestation and delivery at 38 weeks 6 days' gestation. The mother was monitored weekly for obstetric health and drug-related side effects, and the fetus was monitored for growth, activity, and anatomical development by means of ultrasonography. Risdiplam was subsequently administered orally to the infant 8 days after birth and has been continued daily to the present time (30 months of age in February 2025).

The risdiplam concentration and SMN and neurofilament levels were assessed in maternal and infant blood and amniotic fluid at birth. Steady-state trough plasma levels of risdiplam in the mother were approximately 14 ng per milliliter. As compared with maternal plasma concentrations, the drug concentration at delivery was 33% in amniotic fluid and 69% in cord blood. Serial measurements of SMN in blood samples and of light chain and phosphorylated heavy chain forms of neurofilament in plasma samples obtained from the mother and infant are summarized in Table 1.

The infant appeared normal at birth but was identified postnatally to have a heart murmur due to a ventricular septal defect, which resolved. The infant also has mildly reduced visual acuity with transient fixation nystagmus attributed to optic-nerve hypoplasia in both eyes and has mild right hemiparesis associated with left midbrain hypoplasia. Global developmental delay without regression has also been present in the infant to date. Microarray and long-read genome sequencing did not identify a second genetic disorder, such as variants of *HESX1*, *OTX2*, and *SOX2*, which are genes associated with septo-optic dysplasia and neuroendocrine disorders.

No features of SMA, such as hypotonia, weakness, areflexia, or fasciculation, have appeared to date. Motor-function, muscle ultrasonographic, and electrophysiological studies have been performed every 6 months and have shown normal peripheral-nerve and muscle development for age (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Risdiplam was administered to a fetus with SMA by means of oral administration to the mother, with subsequent administration to the child through 30 months of age, and treatment was associated with the absence of manifestations of SMA. Increased SMN levels and reduced neurofilament levels support target engagement of the agent and an effect on motor-neuron development.[2,5] The congenital abnormalities were considered by the investigators to have occurred early in fetal development, before exposure to risdiplam, and no cause has been identified; these changes have not been observed in animals that were administered risdiplam during prenatal and

Table 1. Pharmacokinetic and Pharmacodynamic Studies in the Mother and Infant.*

Variable	Pregnancy†				At Delivery	Postnatal Period					
	32 Wk 5 Days' Gestation	32 Wk 6 Days' Gestation	36 Wk 0 Days' Gestation	37 Wk 6 Days' Gestation	38 Wk 6 Days' Gestation	8 Days	20 Days	29 Days	43 Days	9 Mo	18 Mo
Risdiplam (ng/ml)											
Mother	<LQ	5.3	12.1	14.3	15.6; Amniotic fluid, 5.1	—	0.7	0.6	0.4	—	—
Infant	—	—	—	—	Umbilical vein, 11.2; umbilical artery, 10.4	0.6	—	—	61.5	—	—
SMN (ng/ml)											
Mother	7.7	—	6.3	6.0	4.0	—	5.0	5.1	4.6	—	—
Infant‡	—	—	—	—	Umbilical vein, 9.4	4.5	—	—	6.1	—	—
Neurofilaments in plasma (pg/ml)											
Mother											
Light chain	10.5	10.4	8.8	13.9	12.3	—	19.6	12.7	14.7	—	—
Phosphorylated heavy chain	22	30	26	38	51	—	73	70	62	—	—
Infant											
Light chain	—	—	—	—	Umbilical vein, 8.8; day 1 after birth, 14.4	18.3	—	—	11.4	—	—
Phosphorylated heavy chain§	—	—	—	—	Umbilical vein, 293; day 1 after birth, 313	289	—	—	340	474	240

* Values are from peripheral venous blood samples except as noted. LQ denotes limit of quantification of the assay, and SMN survival motor neuron.
† The samples at 32 weeks 5 days' gestation were obtained before the first dose of risdiplam. The samples at 32 weeks 6 days' gestation were obtained 23 hours after the receipt of the first dose.
‡ In the FIREFISH study, which involved symptomatic infants with spinal muscular atrophy (SMA), at a median age of 6.7 months (range, 3.3 to 6.9), the median concentration of SMN in whole blood was 1.31 ng per milliliter (range, 0.58 to 4.82) in the low-dose cohort and 2.54 ng per milliliter (range, 1.10 to 6.40) in the high-dose cohort.[2]
§ Neurofilament levels that have been reported in typically developing infants (0 to 360 days of age) are as follows: light chain, up to approximately 20 pg per milliliter; and phosphorylated heavy chain, up to approximately 1000 pg per milliliter.[5] In infants with SMA who have two copies of *SMN2*, the typical levels are as follows: light chain, up to approximately 1100 pg per milliliter, with an approximate median level of 200 pg per milliliter; and phosphorylated heavy chain, up to approximately 30,000 pg per milliliter, with an approximate median level of 8000 pg per milliliter.[5]

postnatal development.[4] Results in this single case cannot be generalized but may support the consideration of prenatal risdiplam treatment for SMA identified in utero.

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