BRIEF REPORT

Prenatal Correction of X-Linked Hypohidrotic Ectodermal Dysplasia

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SUMMARY

Genetic deficiency of ectodysplasin A (EDA) causes X-linked hypohidrotic ectodermal dysplasia (XLHED), in which the development of sweat glands is irreversibly impaired, an condition that can lead to life-threatening hyperthermia. We observed normal development of mouse fetuses with *Eda* mutations after they had been exposed in utero to a recombinant protein that includes the receptor-binding domain of EDA. We administered this protein intraamniotically to two affected human twins at gestational weeks 26 and 31 and to a single affected human fetus at gestational week 26; the infants, born in week 33 (twins) and week 39 (singleton), were able to sweat normally, and XLHED-related illness had not developed by 14 to 22 months of age. (Funded by Edimer Pharmaceuticals and others.)

During embryonic development, tissues and organs form in spatiotemporally defined successions of events until the organism has acquired its final shape. Many of these events, such as limb morphogenesis[1] or the formation of sweat glands and other skin appendages,[2] can be irreversibly affected if specific signals are not provided at the appropriate time. For example, deficiency of EDA, which results from loss-of-function variants of the gene *EDA*, causes XLHED (Online Mendelian Inheritance in Man number, 305100).[3] When recombinant Fc-EDA (a fusion protein made up of the constant domain of IgG1 and the receptor-binding portion of EDA) or an antibody that activates the EDA receptor (EDAR) was administered repeatedly into the circulation of pregnant Eda-deficient mice, the disease phenotype of the pups was corrected, yet the dams (which were homozygous for the loss-of-function *Eda* allele) did not benefit from treatment.[4,5] The same was true when Fc-EDA was delivered directly into the amniotic fluid surrounding Eda-deficient fetuses.[6] In the second approach, a single dose was sufficient to correct the disease phenotype, and maternal drug exposure was negligible.[6] Here, we present data supporting a critical role of the neonatal Fc receptor in drug uptake from amniotic fluid. This receptor mediates uptake of IgG from mother's milk across the gut endothelium in rodents.[7] We also report the sustained restoration of sweating ability in three human patients with XLHED in response to prenatal treatment with Fc-EDA.

CASE REPORTS: PATIENTS 1 AND 2

A 38-year-old pregnant woman with a family history of XLHED who was referred to us in gestational week 22 was concerned that the twins she was carrying would

be affected. Her older son had the disease, including a complete absence of sweat pores and sweating; genetic testing revealed hemizygosity for the *EDA* mutation c.911A→G (p.Y304C). Y304 mediates the trimerization of EDA, and its replacement by cysteine abrogates secretion of the protein (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The mother was confirmed to be a heterozygous carrier of this mutation. Ultrasonographic examination showed a twin pregnancy (monochorionic, diamniotic) with two male fetuses, both lacking tooth germs (no tooth germs at all were detected in the mandible and 1 and 2, respectively, were detected in the maxilla; normally, 9 to 10 tooth germs are present in each).[8] Apart from the lack of tooth germs, no anomalies were evident. Additional magnetic resonance imaging (MRI) confirmed the ultrasonographic findings and supported a diagnosis of XLHED in both twins.

The inability to sweat, the most severe clinical problem among patients with XLHED, can lead to life-threatening hyperthermia after birth.[9-11] Given that human sweat glands form between gestational weeks 20 and 30,[12] that sweat-gland development was not rescued by administration of Fc-EDA shortly after birth in patients with XLHED in a previous trial (ClinicalTrials.gov number, NCT01775462), and that delivery of Fc-EDA into the amniotic cavity prevented XLHED in rodents, direct intraamniotic administration of the drug at the appropriate stages of development appeared to be a promising therapeutic approach. We hypothesized that amniotic fluid would serve as a reservoir of Fc-EDA: the size of the protein would limit its diffusion from the amniotic cavity and allow its uptake from the fetal gut through the ingestion of amniotic fluid.

Compassionate use of Fc-EDA requested by the parents of the affected twins was taken into consideration and finally approved by the clinical ethics committee of the University Hospital Erlangen. The parents agreed to intraamniotic administration of Fc-EDA and provided written informed consent. Treatment was to be performed through amniocentesis at week 26 of gestation under ultrasonographic guidance with the same batch of Fc-EDA that had been used in the previous clinical trial. The planned procedure included withdrawal of 15 ml of amniotic fluid, followed by injection of Fc-EDA (100 mg per kilogram of estimated fetal body weight) in a 15-ml sterile solution into the amniotic cavity of each fetus (at 26 weeks, the volume of amniotic fluid is usually >500 ml). A second administration of the drug at 31 weeks of gestation was considered. The EDA concentrations in serum samples from the pregnant woman and treated children and in amniotic fluid were to be determined by a contract research organization (MPI Research).

The academic authors conceived the project, designed the experiments, wrote the first draft of the manuscript, performed and analyzed the experiments in animals, and treated and performed the analysis involving the human patients. The author who is employed by Edimer Pharmaceuticals provided essential materials and assistance with the initial experiments. All the authors reviewed the results, approved the final version of the manuscript, and vouch for the accuracy and completeness of the data presented in this report.

MECHANISM OF DRUG UPTAKE IN A RODENT MODEL

Fc-EDA (EDI200, Edimer Pharmaceuticals) is a recombinant fusion protein consisting of the receptor-binding domain of EDA (100% conserved between the mouse and human proteins) and the Fc domain of human IgG1. When administered at doses of approximately 100 mg per kilogram into the amniotic fluid of male $Eda^{Y/-}$ mice or of $Eda^{-/-}$ mice (either sex) at embryonic day 14.5, Fc-EDA prevented the development of XLHED. In contrast, administration of a control protein that was made up of the same domain of EDA but fused to the collagen-like domain of adiponectin did not prevent XLHED, except in two cases (in one of three pregnancies), which could be explained by accidental introduction of the fusion protein into the fetal bloodstream through damage to the fetus or a peripheral yolk-sac vessel with the injection needle (Table 1, and Table S1 in the Supplementary Appendix). Furthermore, Eda-deficient fetuses that were also devoid of the neonatal Fc receptor did not have their condition corrected by Fc-EDA administered at embryonic day 13.5, whereas all fetuses with expression of the neonatal Fc receptor in the same litter had correction: they developed into mice with only a few remnants of the disease phenotype (Table 1). The same was true for treatment at embryonic day 12.5, except that structures (e.g., guard hair) that formed close to the time of injection were

Table 1. Phenotypic Reversion of Ectodysplasin A (EDA)–Deficient Mice after Administration of Fc-EDA.*

Drug†	Dose	Administration		*Fcgrt* Genotype‡		No. of Mice	Mean Score§				
		Timing¶	Route	Dam	Pup		Teeth‖	Guard Hair**	Ear Hair††	Tail Hair‡‡	Sweat Ducts§§
Fc-EDA	35 μg	E14.5	IA	+/+	+/+	18	2.56	3.00	3.00	3.00	2.94
ACRP-EDA	35 μg	E14.5	IA	+/+	+/+	11	0	0.36	0.27	0.27	0.11
ACRP-EDA	4 mg/kg	P1	IP	+/+	+/+	3	ND	ND	ND	2.67	2.67
ACRP-EDA	1 mg/kg	P1	IP	+/+	+/+	4	ND	ND	ND	2.25	2.75
Fc-EDA	58 μg	E13.5	IA	+/+	+/+	3	2.00	3.00	3.00	3.00	3.00
Fc-EDA	58 μg	E13.5	IA	−/−	−/−	11	0.10	0.36	0	0	0.05
Fc-EDA	58 μg	E13.5	IA	−/−	+/−	5	1.80	3.00	3.00	2.20	1.40
Fc-EDA	58 μg	E12.5	IA	−/−	−/−	5	0	0.20	0	0	0
Fc-EDA	58 μg	E12.5	IA	−/−	+/−	2	1.25	3.00	3.00	0.75	0.25
mAbEDAR1	10 mg/kg	P1, P2, and P3	IP to dam	−/−	−/−	7	ND	ND	ND	0.36	0.29
mAbEDAR1	10 mg/kg	P1, P2, and P3	IP to dam	−/−	+/−	9	ND	ND	ND	2.78	2.89
Fc-EDA	10 mg/kg	P1, P2, and P3	IP to dam	−/−	−/−	8	ND	ND	ND	0	0
Fc-EDA	10 mg/kg	P1, P2, and P3	IP to dam	−/−	+/−	6	ND	ND	ND	0.33	0.67

* IA denotes intraamniotic, and IP intraperitoneal.
† Fc-EDA is a fusion protein made up of the constant domain of IgG1 and the receptor-binding portion of EDA; ACRP-EDA (used as a control) is an active recombinant EDA molecule in which the constant domain of IgG1 that is present in Fc-EDA has been replaced with the collagen-like domain of adiponectin; and mAbEDAR1 is an antibody against the EDA receptor (EDAR).
‡ All the mice were Eda-deficient as a result of carrying the *Tabby* allele (i.e., deletion of exon 1 of *Eda*). Females are *Tabby*/*Tabby*, and males are *Tabby*/Y. *Fcgrt* encodes the neonatal Fc receptor; minus signs indicate a null allele.
§ The scores shown are the mean scores among the indicated number of mice. Treatment after birth does not rescue the development of teeth, guard hair, or ear hair[4]; therefore, these scores were not determined (ND) for mice that were treated after birth.
¶ E preceding a number indicates an embryonic day, and P indicates a postnatal day.
‖ The score for teeth (excluding the third molar) was assigned as follows: 0, narrow molars, shallow cusps, no or rudimentary anterior cusp on the first molar (M1); 1, wider molars, more defined cusps, one small anterior cusp on M1; 2, wide molars, well-defined cusps, stubby anterior cusp on M1; and 3, similar to a score of 2 but with an elongated anterior cusp on M1 (making up approximately one third of the length).
** The guard-hair score (evaluated on a photograph of the back of the mouse) was assigned as follows: 0, no guard hair; 1, between one and five guard hairs visible; 2, sparse guard hair; and 3, numerous guard hairs.
†† The ear-hair score (with the skin area at the rear side of the ears evaluated) was assigned as follows: 0, no hair, naked skin; 1, very few hairs; 2, sparse hair; and 3, dense hair, skin covered.
‡‡ The tail-hair score was assigned as follows: 0, no hair; 1, sparse hair on only one side of the tail; 2, hair on both sides of the tail, usually dense on one side and sparse on the other; and 3, dense hair on both sides of the tail.
§§ The sweat-duct score (evaluated on a photograph of the paw showing all six foot pads after starch–iodine staining) was assigned as follows: 0, no sweat spot; 1, few spots on at least one foot pad; 2, several spots on three or more foot pads; and 3, numerous sweat spots on at least five foot pads.

rescued more efficiently than those (e.g., tail hair and sweat ducts) that formed at later stages of development (Table 1, and Fig. S2 in the Supplementary Appendix).

The fact that Fc-EDA rescued normal development only in the presence of intact neonatal Fc receptor indicates that the therapeutic route of Fc-EDA is systemic rather than direct (i.e., through an effect on the skin and oral epithelia). Moreover, the milk of dams who received an intraperitoneal injection of agonist anti-EDAR antibody (mAbEDAR1) at day 1, 2, or 3 of lactation tested positive for the antibody (Fig. S3 in the Supplementary Appendix). Normal development of the tail hair and sweat glands in Eda-deficient pups that were fed on this milk occurred only if they had expression of the neonatal Fc receptor, which was indicative of neonatal Fc receptor–mediated uptake of this antibody in the gut (Table 1).[13] Bypassing the need for transport mediated by the neonatal Fc receptor through direct intraperitoneal administration of mAbEDAR1 to newborn pups rescued normal development of the tail hair and sweat glands: the efficacy of rescue was the same regardless of whether the neonatal Fc receptor was expressed (Fig. S4 in the Supple-

mentary Appendix). In contrast, intraperitoneal delivery of Fc-EDA to EDA-deficient animals had much stronger effects on neonatal Fc receptor–positive pups than on pups without expression of the Fc receptor. This finding is consistent with the dramatic difference in the half-life of Fc-EDA in serum after intravenous injection between adult mice with a single wild-type allele of the neonatal Fc receptor (48 hours) and adult mice with a complete deficiency of this receptor (22 minutes) (Fig. S5 in the Supplementary Appendix).

The serum half-life of mAbEDAR1 was longer than that of Fc-EDA: 10 days in adult mice with a single wild-type allele of the neonatal Fc receptor and 1 day in null mice. The surprising efficacy of mAbEDAR1 in the absence of neonatal Fc receptor might be explained by the fact that exposure to EDAR agonists (delivered by intraperitoneal injection) for only 4 hours is sufficient to permanently correct the tail-hair phenotype in newborn EDA-deficient mice[14] and because mAbEDAR1, once bound to EDAR, dissociates from it very slowly.[5]

We concluded from these experiments that Fc-EDA provided in amniotic fluid must first enter the organism in a manner that is dependent on the neonatal Fc receptor, presumably through the gut, before it can act on developing EDA-dependent structures. The increased serum half-life of Fc-EDA in the presence of the neonatal Fc receptor further enhances its efficacy.

PRECLINICAL TESTING IN NONHUMAN PRIMATES

Before the decision on the compassionate use of Fc-EDA to treat human fetuses, toxicity studies involving cynomolgus monkeys had been conducted (twice-weekly intravenous infusion of Fc-EDA over a period of 3 weeks followed by a 15-day recovery period). We did not observe signs of toxicity, including at the highest dose (100 mg per kilogram). Another study involving pregnant monkeys showed that transplacental passage of Fc-EDA after intravenous administration to the mother occurred only at very low levels (<1% of concurrent maternal serum concentrations) during the equivalent of the human third trimester (Table S2 in the Supplementary Appendix), which suggested that delivery of the drug to primate fetuses through the maternal circulation may not be an adequate method.

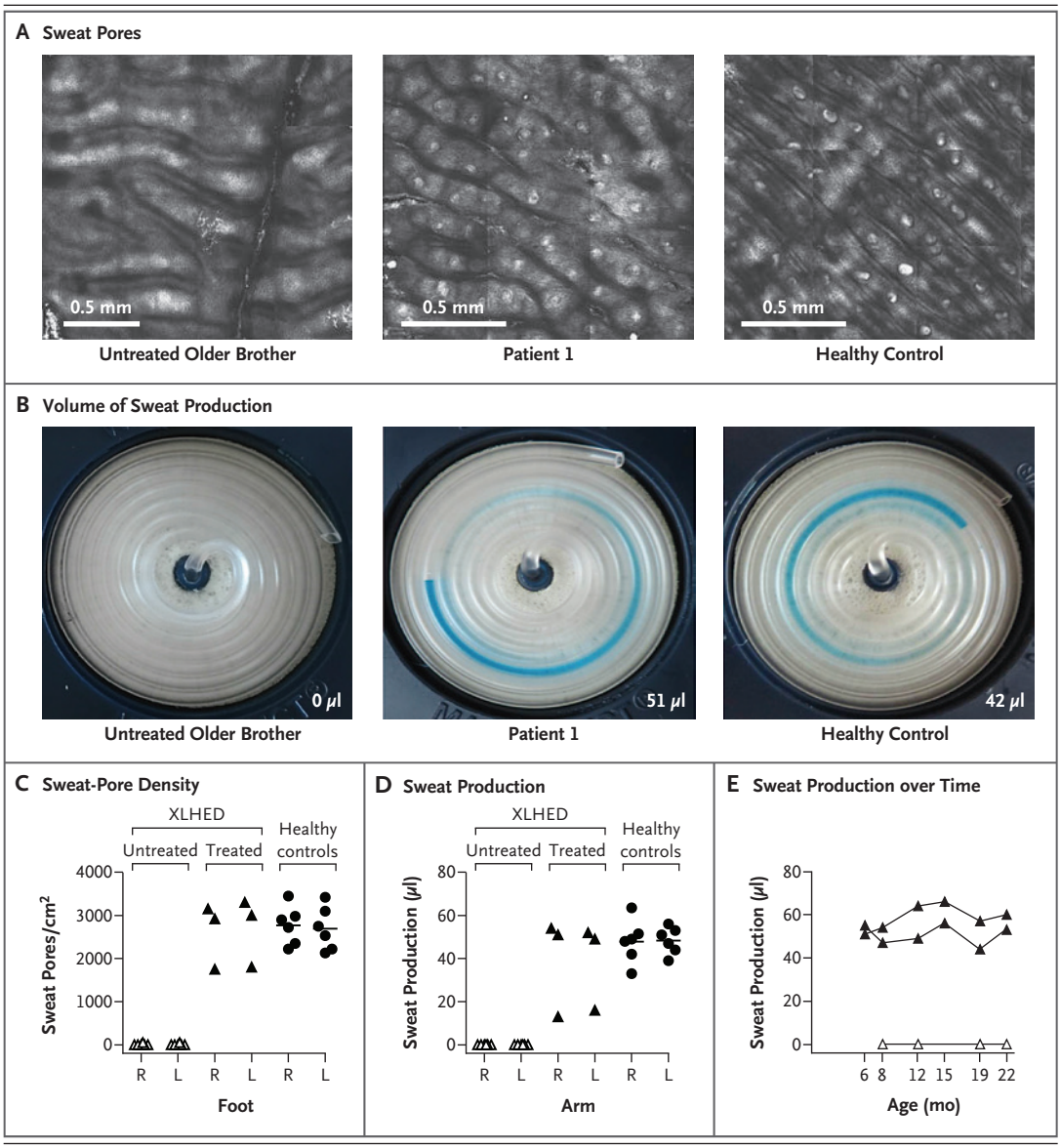
ADMINISTRATION OF FC-EDA TO HUMAN PATIENTS

PATIENTS 1 AND 2

In February 2016, at week 26 of gestation, the affected twins were treated in utero. Amniocentesis of both amniotic cavities was performed to obtain amniotic fluid for genetic testing and to inject Fc-EDA at a dose of 100 mg per kilogram of estimated fetal body weight. In the hours after administration and during the following day, no Fc-EDA was detectable in the circulation of the pregnant woman. The subsequent development of the fetuses was uncomplicated. Genetic testing confirmed the hemizygosity of both twins for the *EDA* Y304C mutation. At week 31 of gestation, 39 days after the first Fc-EDA administration, we injected a second dose of Fc-EDA (100 mg per kilogram of estimated fetal body weight). Assays of Fc-EDA in samples of amniotic fluid that were drawn before the second injection gave a null result.

The twins' mother went into premature labor, and the treated twins were born prematurely by cesarean section on the first day of gestational week 33, with birth weights of 1705 g and 1615 g; at 1, 5, and 10 minutes after delivery, one twin had Apgar scores of 8, 9, and 9, respectively, and the other had scores of 9, 10, and 10. Although the clinical assessment performed after birth did not reveal signs of infection, both neonates received antibiotic agents for 5 days. The neonatal course was unremarkable. In cord-blood samples (one from each twin), Fc-EDA was still detectable 7 days after administration, at concentrations of 62.4 and 932 ng per milliliter, which suggested that it had been taken up continuously from amniotic fluid into the fetal blood.

The treated infants had a normal sweat-duct density[15] on the soles of the feet (Fig. 1A and 1C), as well as normal pilocarpine-induced sweating at 6 months of age (Fig. 1B and 1D). Various body parts were repeatedly observed to be moist. On stimulation with pilocarpine or in the absence of stimulation, Patients 1 and 2 produced amounts of sweat similar to those produced by healthy control infants (Fig. 1E, and Fig. S6A in the Supplementary Appendix), whereas their untreated older brother did not sweat at all. During the first 22 months after birth (including two summers), the twins had no hyperthermic episodes or respiratory-related hospitalizations. They also produced nor-



mal amounts of saliva (Fig. S6B in the Supplementary Appendix). Transillumination revealed 3 to 5 and 6 to 7 meibomian-gland ducts per lower eyelid in Patient 1 and Patient 2, respectively, but only a single gland duct in their untreated brother. No obvious effect of the drug on hypotrichosis was observed. Postnatal MRI and radiographic imaging revealed the presence of 10 and 8 tooth germs in the twins, respectively (Fig. 2), as compared with 3 teeth and 1 additional tooth germ in their untreated brother at 5 years of age.

PATIENT 3

Another pregnant woman who had a son with XLHED was referred to us at week 19 of gestation. Ultrasonography revealed an obvious lack of tooth germs in the male fetus. The parents requested compassionate use of Fc-EDA. This case was also considered and approved by the clinical ethics committee of the University Hospital Erlangen, and the parents agreed to the prenatal procedure and provided written informed consent. The limited supply of Fc-EDA mandated a single dose, which was administered at gestational week 26 into the amniotic cavity. Again, no Fc-EDA could be detected in the maternal circulation within 24 hours after administration of the drug. Genetic testing of fetal cells confirmed hemizygosity for the *EDA* mutation c.924+1dupG (p.V309GfsX8). The subsequent pregnancy and

Figure 1 (facing page). Normalization of Sweat-Gland Development in Patients with X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) Treated in Utero.

Panel A shows the absence of sweat pores (brighter circular spots in the middle of dermal ridges) in the soles of an untreated 3-year-old boy with XLHED (left) and the sweat-pore densities of one of his treated siblings at 6 months of age (middle) and an age-matched male control infant (right). Panel B shows pilocarpine-induced sweat production in the untreated affected brother (left), as well as in one of his treated siblings at 6 months of age (middle) and an age-matched male control infant (right), as measured with a disposable microbore tubing spiral (Macroduct Sweat Collector) placed over the stimulated area of the skin. A small amount of blue dye facilitated quantification of the sweat volume that accumulated over the course of 30 minutes. Panel C shows the sweat-pore density 1 week after the expected date of delivery in all three boys with mutation Y304C or V309GfsX8 in the gene encoding ectodysplasin A (*EDA*) who had received prenatal treatment with Fc-EDA, a fusion protein made up of the constant domain of IgG1 and the receptor-binding portion of EDA (solid triangles), as well as in untreated male patients with the same mutations (age range, 6 months to 21 years) (open triangles) and a group of six healthy control infants who were age-matched to the treated infants (solid circles). The sweat-pore density in the treated infants was similar to that in healthy male infants. The horizontal lines indicate the mean among the controls. L denotes left, and R right. Panels D and E show sweat production in the untreated patients and the treated infants with *EDA* mutations, as well as in healthy controls who were age-matched to the treated infants. In the two infants who received repeated prenatal treatment (Patients 1 and 2), induced sweat production was normal at the age of 6 months (Panel D, upper solid triangles). The horizontal lines in Panel D indicate the mean among the controls. Panel E shows changes in sweat production over time in Patients 1 and 2 (solid triangles) and in their untreated older brother (open triangles). In Patients 1 and 2, sweat production remained in the normal range until the end of the observation period. Details regarding the untreated patients and healthy controls are provided in the Methods section in the Supplementary Appendix.

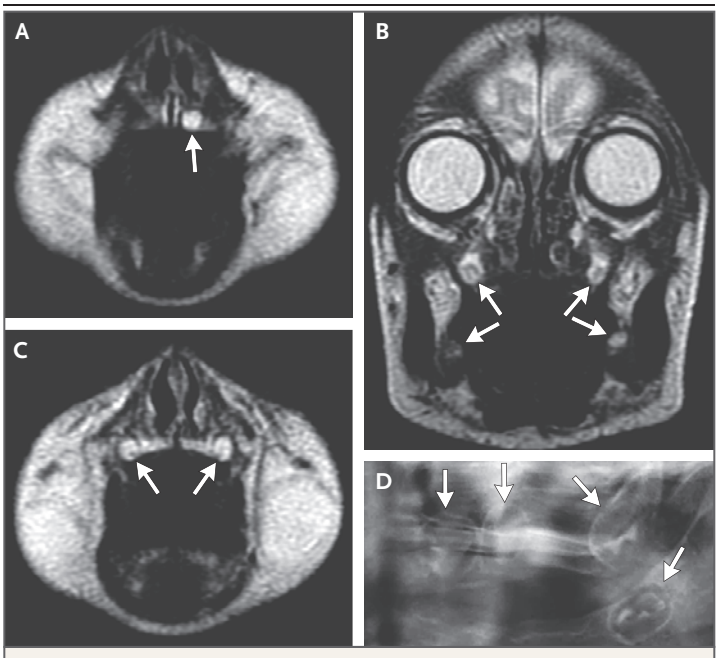


Figure 2. Tooth Germs in One of the Patients Treated in Utero (Patient 1).

Panels A, B, and C are MRI scans showing the tooth buds (arrows) of the left maxillary central incisor (Panel A), the maxillary and the mandibular central molars (Panel B), and two maxillary lateral incisors (Panel C). Panel D is a dental radiograph of the left maxillary region. Tooth germs (arrows) of the upper left incisors and the upper left central molar as well as the mandibular central molar can be recognized as alveolar structures containing calcified tooth components.

delivery were uncomplicated. The treated boy was born in gestational week 39 (Apgar score of 10 at 1, 5, and 10 minutes after delivery; birth weight, 3460 g); he had 1778 and 1822 sweat pores per square centimeter on the soles of his feet, slightly fewer than healthy controls (Fig. 1C). When the patient was 4 months of age, moderate urticaria pigmentosa developed.

Pilocarpine-induced sweat production in Patient 3 at 6 months of age was lower than that in Patients 1 and 2 (Fig. 1D), which suggested slower maturation of sweat-gland function.[16] In contrast to untreated male patients with XLHED, who usually have no more than 3 meibomian glands per eyelid,[17] Patient 3 had a near-normal number of meibomian glands (15 and 11 gland ducts per lower eyelid).[17] Radiographic imaging of the mandible and maxilla revealed the presence of 9 tooth germs; his 2-year-old brother had only 2 tooth buds.

DISCUSSION

Prenatal treatment with Fc-EDA restored sustained sweating ability in human patients with *EDA* mutations that abrogate perspiration. As yet, the treated children, who are now 14 to 22 months old, have not been reported to have had any hyperthermic episodes, nor have they had respiratory-related hospitalizations. Premature labor and preterm birth were severe adverse events. We note that most twins are born preterm and that 20% of twins are delivered before 34 weeks of gestation in the absence of prenatal procedures.[18] The other adverse events in both the women and

their children were moderate or mild (Table S3 in the Supplementary Appendix). Signs of positive effects on tooth development and salivary and meibomian glands have been observed in the treated infants, as compared with the phenotypes of their untreated affected siblings. We do not know whether the therapeutic effects are permanent. We have, however, observed permanent effects in mouse and dog models.[4-6,19,20]

Although the rate of amniocentesis-related miscarriage is only 0.11%,[21] Fc-EDA was not delivered before week 26 of gestation. We reasoned that if inadvertent rupture of membranes occurred at that time, it would probably be possible to prolong the pregnancy for several days or even weeks.[22] In our opinion, the prospects of higher efficacy that could be obtained through earlier treatment do not outweigh even a very low risk of miscarriage. Any preterm birth caused by the procedure would be associated with risks to the baby and the mother (i.e., an increased risk of neonatal illness or death and of maternal infection).

In summary, we identified a mechanism of drug uptake into fetuses, which resulted in effective treatment of a genetic disability, albeit in a very small sample (two pregnancies) and with limited follow-up of the live-born infants. Combined with the ability to identify affected fetuses through noninvasive sonographic prenatal screening,[23] the approach we describe here represents a new means of protein-replacement therapy to correct XLHED.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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