Farmacia Hospitalaria 50 (2026) T204–T207

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Case report

[Translated article] Multidisciplinary approach to prenatal cystic fibrosis with cystic fibrosis transmembrane regulator modulators: Experience in a clinical case

Abordaje multidisciplinar de la fibrosis quística prenatal con moduladores del regulador de la conductancia transmembrana de la fibrosis quística: experiencia en un caso clínico

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Introduction

Cystic fibrosis (CF) is a rare disease, yet it is considered one of the most prevalent autosomal recessive diseases in Europe and the United States.[1] The condition is caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene.[2]

In recent years, treatments that modulate the CFTR protein have been developed. There are two types of modulators: correctors (e.g. elexacaftor, tezacaftor and lumacaftor) and potentiators (e.g. ivacaftor).[3] In Spain, the following treatments are available: monotherapy with ivacaftor is marketed for patients over 4 months of age with class III mutations; triple therapy with ivacaftor, tezacaftor, and elexacaftor (IVA/TEZ/ELX) for patients over 2 years of age with at least 1 F508del mutation in 2 of their alleles; and dual therapy with lumacaftor or tezacaftor with ivacaftor (LUM/IVA or TEZ/IVA). Dual therapy with TEZ/IVA is recommended for patients over 6 years of age, while LUM/IVA is recommended for F508del homozygotes over 1 year of age. Therefore, none of the treatments are recommended for use before the age of 1 year, except for ivacaftor, which is only recommended for a very small group of patients.

We present the case of a patient with a prenatal diagnosis of CF who commenced treatment with CFTR-modulating therapy in utero.

Case description

A 32-year-old woman attended a pregnancy check-up during which an ultrasound revealed a hyperechoic intestine in the foetus at 21 weeks (2nd trimester). During the follow-up examination, dilation of the foetal large intestine was observed in the transverse and descending colon, accompanied by poor peristaltic movement. This obstruction and dilation of the intestinal walls can result in intrauterine complications, such as intestinal perforation leading to meconium peritonitis, or polyhydramnios. A genetic study showed that both parents were carriers of the F508del *CFTR* mutation. At 26 + 2 weeks of gestation, amniocentesis confirmed that the foetus was affected by CF and carried the homozygous F508del CFTR mutation.

To avoid surgery in the neonate and associated complications, alternatives were evaluated by a multidisciplinary team formed by the CF unit and the obstetrics, neonatology, and pharmacy departments. The team proposed treating the pregnant woman with IVA/TEZ/ELX in combination with ivacaftor for meconium ileus detected in the foetus.

Treatment was started at 31 + 1 weeks. The regimen used was for patients of at least 30 kg: 2 tablets of IVA/TEZ/ELX 75/50/100 mg in the morning and 1 tablet of ivacaftor 150 mg at night. During pregnancy, the mother's liver function remained normal, and the only potential adverse effect was a skin rash. A biopsy identified the rash as acute folliculitis. The foetal intestine remained unchanged until week 39, when it was observed that the dilation had resolved (Figs. 1 and 2).[4]

Foetal growth was normal, and spontaneous delivery occurred at 39 weeks, with an appropriate weight for gestational age. The sweat chloride test results were elevated at 80 mmol/L (reference value <60 mmol/L); the faecal elastase concentration was consistent with pancreatic insufficiency at 58.8 μg/g (reference value <100 μg/g); and the immunoreactive trypsinogen level in the heel prick test was normal at 58.1 ng/mL (reference value <60 ng/mL). Despite the presence of these markers, which are characteristic of CF, surgery was avoided in the neonate. From this point onwards, the mother continued the treatment, allowing the drugs to pass into her breast milk so that the neonate could receive them. Breastfeeding ceased at 5 months. However, the neonate could not receive CFTR modulator therapy until 8 months, when the medications were approved for use in this case. Clinical worsening was observed at this point, and treatment was resumed as follows: first, LUM/IVA 75/94 mg oral granules, followed by LUM/IVA 100/125 mg oral granules once the neonate exceeded 9 kg. At 16 months,

DOI of original article: https://doi.org/10.1016/j.farma.2025.09.003.
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https://doi.org/10.1016/j.farma.2025.09.005
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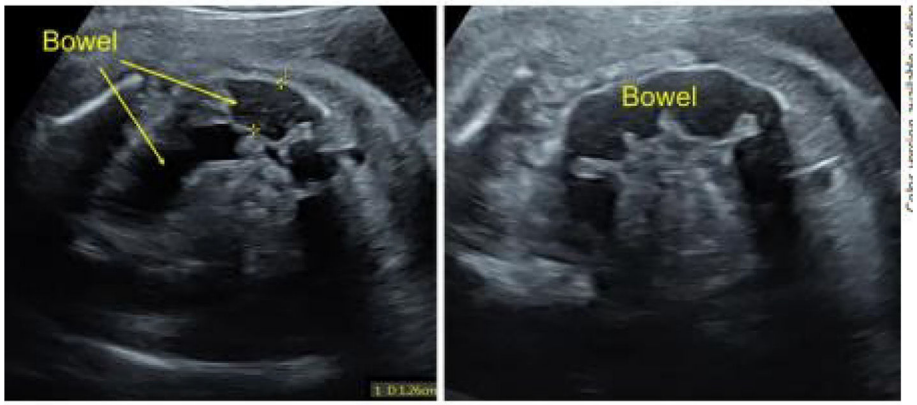

Figure 1. Dilated foetal intestine at 27 weeks of gestation before maternal therapy.

the dual therapy was changed to ELX/TEZ/IVA 80/40/60 mg in the morning and IVA 59.5 mg at night, both treatments in the form of oral granules. The patient is currently 18 months old and continues on this treatment, along with pancreatic enzymes and fat-soluble vitamins. In addition, the patient has an appropriate weight for their age, a good appetite, and tolerates complementary feeding well.

Discussion

This is the first published case in Spain in which CFTR modulators were administered to a healthy mother to treat a foetus affected by CF. This case is notable for its exceptionally early prenatal diagnosis and the prolonged follow-up. These factors enabled an assessment of the effects of treatment during pregnancy, breastfeeding, treatment discontinuation, and reintroduction of the medication in oral form. Treating the foetus through the mother resolved the meconium ileus, thus avoiding surgery in the neonate. Its continued administration via the oral route during and after breastfeeding was effective in preventing infections and facilitating weight gain in the patient, as confirmed by the patient's deterioration during the drug-free period following the end of breastfeeding.

The evidence on the use of CFTR modulators in pregnant women is mixed.[5–7] The case series conducted by Taylor-Cousar et al. was among the first to evaluate the use of CFTR modulators in pregnant women with CF who were carrying healthy foetuses. The authors concluded that the treatment was safe for pregnant women and their foetuses. It is noteworthy that 35 of these patients initiated treatment during the first trimester of pregnancy—the period of organogenesis and the stage of greatest potential risk for malformations—with no congenital anomalies related to the treatment being observed. Similarly, other studies have reported cases in which both the mother and the foetus had a confirmed diagnosis of CF with homozygous F508del mutations. The neonates had a favourable clinical outcome, without complications attributable to the disease, malformations, or adverse effects related to the treatment.[8,9] All of the pregnant women in these studies received triple therapy with IVA/TEZ/ELX.[5,8,9] In our case, triple therapy was chosen over dual therapy with LUM/IVA, which is approved for patients at least 1 year of age, for the following reasons: triple therapy has been proven to be more effective in patients homozygous for the F508del mutation; it demonstrates a better response in resolving meconium ileus; there is published evidence supporting its effectiveness in similar cases; despite not being formally indicated for children under 2 years of age, triple therapy has a favourable risk–benefit ratio.

Based on the scientific evidence available in the literature, treatment with ELX/TEZ/IVA was initially used off-label in pregnant women. Initially, direct administration to the neonate was not considered, as the neonate was still receiving the treatment indirectly through breastfeeding. However, direct therapy was deemed necessary when breastfeeding ceased, the clinical effect was lost, and there was evidence of deterioration in the patient's general condition. Given that ELX/TEZ/IVA was not marketed in Spain for children under 2 years of age at that time, access was arranged through the application for Medicines in Special Situations (MSE) of the Spanish Agency for Medicines and Health Products (AEMPS). To this end, the manufacturing laboratory was contacted to identify international presentations adapted to the patient's weight and age. Subsequently, the authorisation request was

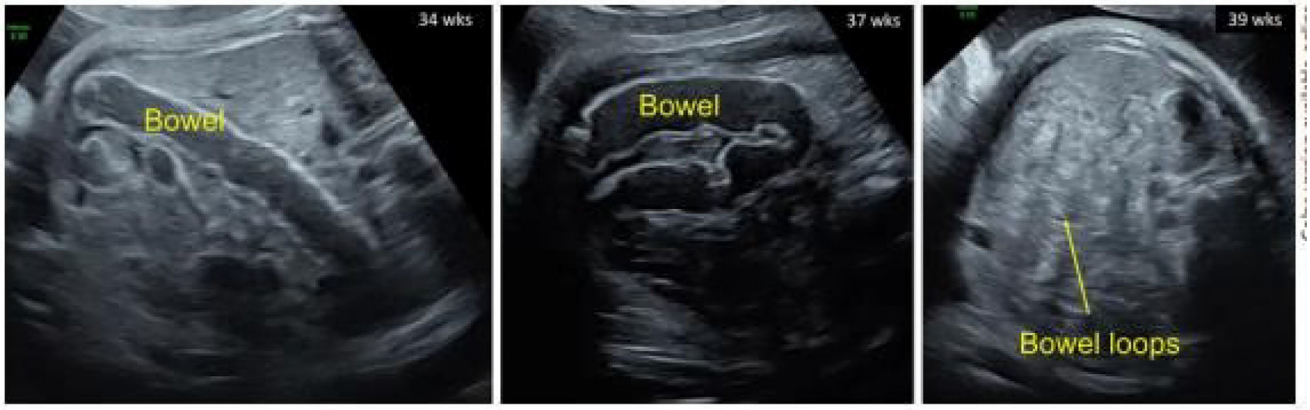

Figure 2. Dilated foetal intestine at 34 and 37 weeks of gestation (3 and 6 weeks after starting maternal therapy, respectively), and resolved dilated foetal intestine at 39 weeks of gestation (8 weeks after starting treatment).

processed through the hospital's medical board and formalised for the AEMPS. This procedure was used to obtain the LUM/IVA and ELX/TEZ/IVA presentations, as these medications are international products officially indicated for older patients, but with a body-weight profile comparable to that of the patient.

In the present case, the therapeutic decision was based on the existing evidence regarding the transplacental passage of CFTR modulators and their excretion in breast milk, as described in other studies.[9–11] The optimal concentration of the drugs in milk is currently unclear. One study found relatively low average concentrations of LUM (0.06 μM) and IVA (0.09 μM) in the breast milk of a mother taking LUM/IVA during pregnancy and lactation; however, the dose used was not specified.[12] This result is consistent with other cases in which ELX/IVA/TEZ concentrations were less than 1 μM in milk samples collected between 15 and 60 days postpartum;[13] in these cases, the doses of modulators administered to the mothers were also not specified. However, drug concentrations in milk reached 1.795 μM in a case involving higher doses of ivacaftor, in which the mother was taking elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg twice daily, as well as an additional dose of ivacaftor 150 mg once daily.[14] This result suggests a possible dose–response relationship. Therefore, the potential effects of these concentrations on infants remain unclear and require further research.[15]

The latest faecal elastase measurements in the patient were 219 and 137 μg/g. This result further supports our hypothesis that the early administration of CF drugs (before 2 years of age) promotes pancreatic recovery. Consequently, delaying the initiation of treatment would not be advisable.

The hospital pharmacy service played a key role throughout the therapeutic process in this case. It actively participated in selecting the most appropriate treatment based on the available scientific evidence, even though it involved off-label use in an exceptional clinical context. The service also coordinated access to these medicines, which are not currently marketed in Spain, via the AEMPS MSE. It also liaised with the manufacturing laboratory, identified international presentations suitable for the patient, and processed the authorisation. In addition, the service collaborated with the clinical team to design the dosage regimen, adapt the formulation to the infant's characteristics, and monitor the treatment in both the mother and the neonate.

The use of CFTR modulators has been shown to significantly improve lung function and quality of life in patients.[16] This has led to an increasing number of cases in which this treatment must be continued during pregnancy. However, clinical case reports have inherent limitations, including selection bias and an absence of systematic data on the efficacy, safety, and pharmacokinetics of these drugs in younger paediatric populations and in exceptional clinical contexts. Thus, although clinical cases have reported the safety of these treatments for both the mother and the foetus, clinical trials involving pregnant patients and children are still required. In line with the latest revision of the Declaration of Helsinki, excluding vulnerable groups, such as pregnant women and young children, from well-structured, controlled studies could perpetuate health disparities; therefore, it is crucial that these groups are included in research to ensure equitable therapeutic advances.[17] Evidence-based treatment guidelines for this vulnerable population require a better understanding of the exposure profile and therapeutic efficacy of these drugs when administered during the prenatal and breastfeeding periods.

Conclusion

Administering CFTR protein modulators during pregnancy and breastfeeding was safe for both mother and her child and effective in treating CF in this patient, helping to avoid neonatal surgery and supporting adequate growth and development. This is the first case in Spain to report on intrauterine treatment using CFTR modulators, as well as follow-up after breastfeeding. It provides valuable information on managing similar situations in clinical practice.

Presentation at conferences

Organisation: Spanish Society of Hospital Pharmacy (69th SEFH Congress). A Coruña (Spain). 17–19 October, 2024.

Contributions

Pedro del Palacio García, Carmen García Muñoz, and María Dolores Canales Siguero collaborated on conceiving the original idea, designing the study, and writing and critically reviewing the article. Maria Carmen Luna Paredes and Enrique Salcedo Lobato collaborated on designing the study and critically reviewing the clinical case. Fernando Huecas Jiménez and Carlota Vaquer Ferrer collaborated on writing, designing, and editing the manuscript. José Miguel Ferrari-Piquero contributed to writing and critically reviewing the article.

All authors approved the final version of the article.

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CRediT authorship contribution statement

Pedro del Palacio-García: Writing – review & editing, Writing – original draft, Visualisation, Validation, Supervision, Methodology, Conceptualization. **Carmen García-Muñoz:** Writing – original draft, Validation, Supervision, Conceptualization. **María Dolores Canales-Siguero:** Writing – original draft, Validation, Supervision, Conceptualization. **Maria Carmen Luna-Paredes:** Writing – review & editing, Writing – original draft, Visualisation, Validation, Supervision. **Enrique Salcedo-Lobato:** Writing – review & editing, Writing – original draft, Visualisation, Validation. **Fernando Huecas-Jiménez:** Writing – review & editing, Supervision. **Carlota Esperanza Vaquer-Ferrer:** Writing – review & editing, Validation, Supervision. **José Miguel Ferrari-Piquero:** Writing – review & editing, Visualisation, Conceptualization.

Funding

None declared.

Conflict of interest

None declared.

Acknowledgements

We would like to express our gratitude to the gynaecology, obstetrics, and neonatology departments for their collaboration.

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