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RESEARCH LETTER

Experience of Tofacitinib Use in Pregnancy in Patients with Ulcerative Colitis

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The management of inflammatory bowel disease during pregnancy poses unique challenges because of the complex interplay between disease activity, medication safety and maternal-foetal well-being. In recent years, tofacitinib has shown efficacy in inducing and maintaining remission in moderate-to-severe ulcerative colitis (UC), leading to its approval for this indication [1]. Despite its clinical benefits, questions arise regarding the safety of tofacitinib for both maternal health and foetal development. Tofacitinib has demonstrated to be teratogenic in animals, and therefore, it is currently not recommended during pregnancy [2, 3]. Consequently, the experience with tofacitinib in pregnant women is scarce.

In this article, we present two cases from the DUMBO Spanish registry [4]: a prospective, observational, and multicentre registry, which enrols pregnant women with inflammatory bowel disease over 5 years in 70 centres, where patients received tofacitinib during pregnancy for UC. Our objective is to provide novel safety data regarding the use of tofacitinib in this critical situation and review the existing literature to enhance the knowledge about the drug's safety during pregnancy in humans. Ultimately, our findings aim to support healthcare professionals in the critical task of balancing the management of UC and the well-being of pregnant patients, aiding in the decision-making process and improving patient outcomes.

The first case was a 24-year-old woman diagnosed with UC in September 2018. In December 2018, she was admitted because of a severe corticorefractory flare of UC and started infliximab in combination with azathioprine, reaching remission. In June 2019, the patient lost response to infliximab and was started on vedolizumab. The patient did not reach remission with vedolizumab (primary failure). In May 2020, a colonoscopy revealed moderate disease activity. In June 2020, tofacitinib was initiated at the standard induction dose of 10 mg twice daily (b.i.d.) for 8 weeks followed by maintenance therapy of 5 mg b.i.d., reaching clinical remission. In May 2022, the tofacitinib dosage had to be escalated to 10 mg b.i.d. because of disease activity. Upon learning about her pregnancy in June 2022, tofacitinib was discontinued. The patient's last menstrual period was documented in April 2022, estimating a gestational age of approximately 5 weeks at the time of tofacitinib withdrawal. Adalimumab was initiated after tofacitinib discontinuation. The patient achieved clinical remission within 4 weeks of treatment initiation. The patient gave birth to a healthy baby boy via a vaginal delivery in March 2023 at 40 weeks of gestation. The newborn did not experience any complications and was in good health after birth.

The second case was a 39-year-old woman diagnosed with UC in 2012. Her adherence to treatments and follow-up was suboptimal from the diagnosis. Prior to initiating treatment with tofacitinib, the patient had received initial therapy with infliximab (experiencing primary treatment failure) and subsequently with vedolizumab. Initially, she responded well to vedolizumab treatment, but later lost response and did not improve after dose intensification. In March 2021, tofacitinib was recommended, and the patient was advised against becoming pregnant. Tofacitinib treatment was initiated at a dose of 10 mg b.i.d., which was extended beyond 8 weeks because of a delayed responder, and remission was eventually achieved.

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In November 2021, the patient reported being pregnant. The contraindications, the limited experience with tofacitinib during pregnancy and the different options in this situation were discussed again with the patient. The patient decided to proceed with the pregnancy and continue treatment with tofacitinib, which was then reduced to a maintenance dose of 5 mg b.i.d. In February 2022, at 18 weeks of gestation, the patient presented with symptoms of an UC flare, plus faecal calprotectin > 6000 µg/g. Her obstetricians recommended her to discontinue tofacitinib treatment, and rectal mesalamine was initiated. Additionally, she experienced a threatened miscarriage. In May 2022, at 33 weeks of gestation, the patient was hospitalised because of a premature rupture of membranes and gave birth to a male infant weighing 1750 g. The baby had polydactyly of his left hand's first finger. Other findings were consistent with his gestational age at birth. The newborn was admitted to the neonatology department, where he experienced some episodes of apnoea and bradycardia on the second day of life, but only required oxygen therapy. The newborn was discharged without complications 25 days after birth.

In this study, we aimed to contribute to the growing body of knowledge regarding the use of tofacitinib in pregnancy through the presentation of two clinical cases. The first case involved a short exposure to tofacitinib during a crucial period in organogenesis, and no adverse events were observed in the newborn. In the second case, tofacitinib exposure occurred during the first 18 weeks of gestation. At that time, the patient experienced a disease flare, which likely contributed to a preterm delivery. The newborn exhibited polydactyly, although the relationship between the condition and the drug remains uncertain.

Tofacitinib, an pan inhibitor of Janus kinases (JAKs), has received approval for the management of conditions such as rheumatoid arthritis, psoriatic arthritis and, more recently, UC. Patients who may desire to have children in the future could be undergoing treatment with tofacitinib, and for this reason it is an utmost need to have information about its risks during pregnancy. On the one hand, in vitro and in vivo investigations have ruled out mutagenic and genotoxic effects of tofacitinib [5]. On the other hand, in animal studies, tofacitinib demonstrated feticidal and teratogenic effects in rats and rabbits at exposures significantly higher than the approved human doses for rheumatoid arthritis and UC: the exposures in these studies were 146 times and 13 times greater than the human dose of 5 mg b.i.d. daily in rats, and 73 times and 6.3 times greater than the human dose of 10 mg b.i.d. in rabbits [5]. The teratogenic effects observed included external and soft-tissue malformations, such as anasarca and membranous ventricular septal defects, as well as skeletal malformations. Additionally, there was an increase in post-implantation loss and a decrease in the number of viable foetuses and mean foetal body weight. However, it is important to note that the extrapolation of these findings to human risk is complex, and predicting the impact of tofacitinib on human pregnancy based solely on these animal studies is challenging.

In this respect, the JAK/STAT pathways play a role in mediating signal transduction for various immunological signals [6], and recent research on rats suggests the involvement of the JAK family in regulating the immune interface between the mother and the foetus within the placenta [7]. However, current evidence is insufficient to form any hypotheses regarding the potential effects of JAK inhibition, particularly during the second and third trimesters, on pregnancy outcomes.

Limited data are available regarding women exposed to tofacitinib at conception and during pregnancy. In 2018, Mahadevan et al. published a study providing information on pregnancy outcomes in patients with UC and other indications from the tofacitinib safety database until March 2017. Authors analysed both data from interventional (randomised clinical trials) and non-interventional studies (post-approval safety studies and spontaneous reporting) [8]. From interventional studies in patients with UC, a total of 25 pregnancy cases were reported, including 11 maternal and 14 paternal exposures [8]. In all 11 maternal cases, tofacitinib exposure began during the first trimester. Most outcomes resulted in healthy newborns ($n = 4$, including one preterm birth at 36 weeks), while two spontaneous abortions and two medical terminations were reported. Two cases had pending outcomes, and one case had an unknown outcome. Among the 14 paternal cases, tofacitinib exposure also occurred during the first trimester in all cases. Eleven healthy newborns were reported, with one case having a pending outcome and two cases lacking follow-up consent.

For the rheumatoid arthritis, psoriasis, and psoriatic arthritis cohorts in interventional studies, a total of 53 cases of maternal exposure to tofacitinib were identified, all of which began during the first trimester [8]. The most common outcome was a healthy newborn ($n = 33$), including three preterm births. One case involved a newborn with a congenital malformation (pulmonary valve stenosis) in a 32-year-old patient with rheumatoid arthritis who had hypertension, was treated with losartan, had gestational diabetes and received tofacitinib (5 mg b.i.d.). Ten spontaneous abortions and 11 medical terminations were reported, while eight maternal exposure cases had pending outcomes or were lost to follow-up. In indications other than UC, there were a total of 70 cases of paternal exposure to tofacitinib [8]. The most common pregnancy outcome was a healthy newborn, with 44 reported cases. There were seven spontaneous abortions and one neonatal death (cardiac arrest). The remaining 18 cases were either pending outcomes or lost to follow-up. The safety database included 45 post-marketing cases of tofacitinib exposure during pregnancy, 42 with maternal exposure

and three with paternal exposure [8]. Among these cases, there were seven healthy newborns, one medical termination, three spontaneous abortions and one congenital malformation. The majority of cases ($n = 33$) were pending outcomes or lost to follow-up.

Overall, the frequencies reported in this study align with the background risk observed in the general population. However, because of the limited number of pregnancy cases reported with tofacitinib, definitive conclusions regarding the impact of tofacitinib on pregnancy and newborn outcomes cannot be drawn, as stated by the authors [8]. More recently, a clinical case of a 40-year-old woman with psoriatic arthritis who became pregnant during the first month of treatment with tofacitinib and in whom tofacitinib was interrupted immediately was reported [9]; at the end of pregnancy, the patient gave birth to a healthy newborn.

Other more selective JAK inhibitors, such as upadacitinib and filgotinib, have recently been approved for the treatment of inflammatory bowel disease and other conditions [10–13]. There are currently no human data available on upadacitinib or filgotinib during pregnancy. In preclinical studies, upadacitinib demonstrated teratogenic effects in both rats and rabbits [14]. Similarly, filgotinib has shown embryotoxicity and teratogenicity in rats and rabbits, leading to malformations in the central nervous, musculoskeletal, respiratory and cardiovascular systems at exposures equivalent to the 200-mg daily dose in humans [15].

With respect to breastfeeding, tofacitinib has been detected in milk after a single dose of 10 mg b.i.d. in lactating rats, with a concentration that is approximately two times higher than in serum [5]. Recently, these results have been confirmed in humans [16]. Similarly, upadacitinib has been found in milk when given to lactating rats, with milk concentrations approximately 30 times higher than plasma concentrations. In the case of filgotinib, it has been identified also in nursing pups following its administration to lactating rats [14, 15]. For these reasons, breastfeeding is contraindicated in patients treated with all JAK inhibitors [3].

In conclusion, tofacitinib and other JAK inhibitors are currently contraindicated during pregnancy and lactation. When planning a pregnancy, it is recommended to discontinue tofacitinib and upadacitinib at least 4 weeks before conception [5, 14], while a 1-week wash-out period is recommended for filgotinib [15]. In the event of an unintended pregnancy leading to exposure to tofacitinib, it is essential to engage in a comprehensive discussion regarding the benefits and risks involved. This discussion should involve the patient, their family and healthcare professionals who are knowledgeable and suitable for providing guidance. Sharing the experience with these drugs in pregnancies occurring in clinical trials and clinical practice will help to understand their safety in this complex clinical situation.

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Declarations

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Conflict of interest María Chaparro has served as a speaker and consultant for and has received research or education funding from MSD, AbbVie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Biogen, Gilead and Lilly. Raquel Vicente has served as an advisor for and has received research support and/or training activities from AbbVie, Janssen, MSD, Pfizer, FAES-FARMA, Ferring, Shire and Takeda. Javier P. Gisbert has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma. Daniel Ceballos has no conflict of interest to declare.

Ethics approval All procedures in this study were in accordance with the 1964 Helsinki Declaration (and its amendments). The study was approved by the Ethics Committee of Hospital Universitario de La Princesa in August 2018.

Consent to participate All patients provided consent to participate in the study.

Consent for publication Not applicable.

Availability of data and material The data underlying this article will be shared on reasonable request to the corresponding author.

Code availability Not applicable.

Author contributions MC and JPG: study design, data collection, data interpretation, writing the manuscript. Rest of authors: patient inclusion. All authors approved the final version of the manuscript. MC and JPG are the guarantors of the article.

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