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Safety Prediction of Infants Born to Mothers with Crohn's Disease Treated with Biological Agents in the Late Gestation Period

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Abstract

Objectives: Knowledge gaps exist in the use of biologics for pregnant patients with Crohn's disease (CD), especially the usage of ustekinumab (UST) and infliximab (IFX) infusion during the late gestation period. In this case series, we investigated perinatal and neonatal outcomes and pharmacokinetics of these biologics in pregnant CD patients.

Methods: Pregnant CD patients under treatment with IFX or UST during January 2017 to December 2019 were monitored. Growth and development of their babies were followed up to six months. Drug concentrations were measured in maternal peripheral and cord blood at delivery and infants' blood at six months of age.

Results: Four cases were kept IFX treatment until late gestation (median last dose: 31.2 weeks). One case received UST until 23 weeks of gestation. All cases were in clinical remission but moderately undernourished. Babies were delivered by cesarean section at full term without any complications or congenital abnormalities. No growth or developmental defects and no susceptibility to infections were observed by six months. However, two babies whose mothers received IFX after 30 weeks of gestation were detected IFX in their blood at six months of age (0.94 and 0.24 pg/ml). Concentrations of UST in maternal and cord blood were 267.7 and 756.5 ng/ml, respectively. UST was not detected in the infant at six months of age.

Conclusions: Administration of UST or IFX to pregnant patients with CD is safe, particularly IFX to be given in the late gestation period. Understanding of the pharmacokinetics of biologics in maternal-infant interactions may improve the management of pregnant CD patients.

Keywords

Crohn's disease, biologics, infliximab, ustekinumab, pregnancy, vaccines

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Introduction

Many female patients with inflammatory bowel disease (IBD) become pregnant during active intestinal inflammation. Although many of them can pass the gestation period safely and deliver healthy babies by controlling disease activity, some patients may not maintain remission during pregnancy. A history of bowel resection may result in mal-

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nutrition even in the remission period, which may lead to premature babies and/or babies with low birth weight[1]. To avoid these issues, it is important to select the best treatment option and discuss nutritional management with pregnant patients with IBD on an individual basis. Recently, more female patients with IBD who have been treated with biological agents are continuously receiving the biologics after getting pregnant. Most clinical guidelines highlight the importance of maintaining remission throughout the gestation period for safe childbirth in mothers with IBD[2,3]. Although it is thought that most medications that are used to treat IBD, including biologics, can be prescribed up to the late gestation period or even later in pregnancy[2,3], the safety profile of those situations has yet to be fully established.

Biological agents appear to be as potent treatment options in pregnant as non-pregnant patients with IBD. Anti-tumor necrosis factor α (TNF-α) agents are biological agents that are composed of immunoglobulin G (IgG) against TNF-α. Accumulating evidence has identified that the treatment of pregnant IBD patients with anti-TNF-α agents does not lead to adverse health outcomes in neither the mother nor their newborn baby[4-6]. Even so, the anti-TNF-α agents are recommended for discontinuation by week 26 (before the second trimester ends) because the anti-TNF-α agents are transmitted to infants through the placenta mainly in the late gestation period and may remain in babies for months after birth[2,3]. Live vaccines such as Bacille Calmette-Guerin (BCG) and rotavirus vaccines may therefore bring a risk of inducing infections if those babies carry immunosuppressive biological agents. In fact, fatal cases of disseminated BCG infection following BCG vaccination have been reported in infants exposed to IFX in utero[7,8]. Although it is recommended that live vaccines should be given to those babies after they are six months old, the proper vaccination timing in these cases have not been established. For instances, a recent study shows that anti-TNF-α agents can be detected in babies up to 12 months of age[4]. Taking this fact into account, Italian guidelines suggest that live vaccines should be avoided up to one year of age in babies born to mothers who had received anti-TNF-α treatments[9]. Furthermore, the health outcome and the safety and efficacy of vaccinations in babies born to mothers with IBD who received other biologic agents such as UST, which Inhibits the p40 subunit of interleukin (IL)-12 and IL-23, have not been explored. Because the clearance of biological agents in babies may differ based on the timing of the last prenatal exposure to them, further studies will be needed to detail the optimal timing of live vaccines in babies born to mothers who received the biological agents.

Collaborating with pediatricians, we measured concentrations of IFX and UST in cord blood and peripheral blood of babies born to mothers with Crohn's disease (CD) who received those biologics during and after second trimester. Our results may provide cues to understand for how long biological agents (IFX and UST) remain in infants born to mothers with CD who received them. A better understanding of pharmacokinetics in newborn babies who are exposed to these biologics will determine a proper timing of vaccinations in children of patients with IBD.

Subjects and Methods

Pregnant patients with CD who required either IFX or UST dosing during and after second trimester to control disease activity were enrolled from January 2017 to December 2019 in our institution. Patient demographics, history of gravidity and parity, disease characteristics, and past surgical history were documented. Their disease activity and complications, cycles, and dosing of biologics were monitored until delivery. The presence of abnormalities during pregnancy, perinatal complications, as well as the gestation days that the last dose of the biologics was given were recorded. Serum levels of C-reactive protein (CRP) and albumin were measured at delivery as surrogate markers of inflammatory and nutritional statuses, respectively. Gestational age at birth, mode of delivery, birthweight, and congenital abnormalities were assessed by obstetricians. Concentrations of IFX and UST were measured in maternal peripheral blood (Case 5) and cord blood at delivery (Cases 1 and 5) of the cases from whom we could obtain authorization. Blood samples were taken from the babies (all cases) at six months of age to detect the remaining biologics.

Concentrations of IFX and UST were measured by sensitive TNF-α Enzyme-Linked Immuno Sorbent Assay (ELISA: detection limit: 0.15 pg/ml, SRL, Japan) and IDKmonitor Ustekinumab dug level ELISA, K9660 (detection limit: 0.747 ng/ml, Immundiagnostic GA, Germany), respectively. BCG was given to the babies if the levels of biologics were less than the detection limits. We repeated the measurements of blood levels of biologic drugs in three months in babies who were detected the biologics at six months of age. This study is approved by the institutional review board at the Tokyo Yamate Medical Center. Informed consents were obtained from all patients involved in this study through an opt-out.

Results

Patients' conditions and their treatments during pregnancy

Five CD patients were enrolled, including four cases of IFX (cases 1-4) and a case of UST (case 5). The baseline characteristics of these patients are shown in Table 1. The mean age of patients was 34 (range 3-35) years. One patient was colitis type (case 4) and the remaining four cases were all ileocolitis type. Their disease behavior included one non-

Table 1. Patients' Background of Disease and Condition at Delivery.

	Case 1	Case 2	Case 3	Case 4	Case 5
Biologics	IFX	IFX	IFX	IFX	UST
Age (years)	34	31	35	32	35
Previous delivery	0	1	1	2	1
Lesion of disease	Ileocolitis	Ileocolitis	Ileocolitis	Colitis	Ileocolitis
Disease type	Stenosis/fistulation	Stenosis	Fistulation	Inflammation	Stenosis
Disease duration (years)	15	7	13	2	12
Previous surgery	1	1	1	0	2
Concomitant medication	5ASA, AZA	5ASA	5ASA, ED	none	5ASA, ED
CRP (g/dl) at delivery	0.1	1.1	0	0.2	0.2
Alb (g/dl) at delivery	2.8	3.3	2.9	3.2	2.7
Duration of bio (years)	7.83	0.83	4.33	1	0.33
Dose of bio	10 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg	90 mg
Intervals of bio	6~7w	8w	8w	8w	8w

Table 2. Details of IFX/UST-Administered Births.

	Case 1	Case 2	Case 3	Case 4	Case 5
Discontinuation of bio	32w5d	31w5d	30w4d	26w2d	23w3d
Gestational age at birth	38w0d	38w3d	38w5d	38w3d	38w0d
Delivery method	CS	CS	CS	CS	CS
Apgar score	8	8	8	8	8
Birth weight (g)	3002	3260	3206	3076	2596
Congenital abnormalities	None	None	None	None	None
IFX/UST in mother's blood	Not measured	Not measured	Not measured	Not measured	267.7 ng/ml
IFX/UST in cord blood	36.89 μg/ml	Not measured	Not measured	Not measured	756.5 ng/ml
IFX/UST at 6 months	0.94 pg/ml	Not detected	0.24 pg/ml	Not detected	Not detected

CS: caesarean section

structuring, non-penetrating (inflammatory), two structuring, and one each penetrating or structuring/penetrating types. Besides the case of inflammatory type, all four cases had histories of bowel resection. All cases had anal involvement upon enrollment and case 2 was on colostomy. In terms of the concomitant drugs, most of them were taking 5-aminosalicylic acid (5-ASA) except case 4; cases 3 and 5 which were given enteral nutrition (ED) due to malnutrition, and case 1 was receiving azathioprine (AZA) due to the reduced efficacy of IFX. None of the cases had any underlying diseases other than CD and had no perinatal complications. There were no biological agents administered in these five cases prior to the treatment with IFX (case 1-4) and UST (case 5).

IFX had been administrated for 2.7 ± 3.3 years, and the treatment was continued after 26 weeks of gestation. Case 1 received IFX (10 mg/kg) every 6 to 7 weeks and safely discontinued the treatment 32 weeks and 5 days of gestation. Cases 2 to 4 were treated with IFX (5 mg/kg) every 8 weeks and stopped the infusion in their late gestation periods as shown in Table 1, 2. Case 5 received UST (90 mg/kg) every 8 weeks and discontinued the injection 23 weeks and 3 days of gestation. All these cases were in clinical remission at conception, and two cases (case 2 and 3) were confirmed endoscopic remission within one year before getting pregnant. Except Case 2, whose disease had been kept mildly active (CDAI 150-220 points) during pregnancy, all cases were in clinical remission (CDAI < 150 points). Although serum albumin levels at delivery were as low as 2.9 ± 0.3 g/dl in those patients, no other conditions that could reduce albumin levels, e.g., preeclampsia and hepatic or renal dysfunction, were detected. During the period between the last dose of the biologics and the delivery date, their disease activities remained stable and the differences of CDAI score in each case before and after the discontinuation of the biologics had been kept less than 70 points.

IFX treatment in the late gestation period of CD patients does not induce adverse perinatal outcome but newborn babies may retain IFX for over six months

Although anti-TNF-α agents have been thought to be safe treatment in pregnant patients with IBD[10], the safety and short-term and long-term effects of these agents on the fetuses have not been fully confirmed in cases that these

Table 3. Cases of Pregnancy with CD under UST Treatment.

Diagnosis	Age	Duration of UST treatment	Pregnancy outcome	Postpartum drug levels (μg/ml)	Cord blood drug levels (μg/ml)	Infant's development	Routine vaccination	
CD	28	Until 33rd weeks of gestation	Full-term, healthy	-	-	-	-	Galli-Novak et al. 2016 [19]
CD	37	During all gestation period	Full-term, healthy	-	-	Normal	Done	Cortes et al. 2017 [11]
CD	32	4 weeks	Fetal death in week 4	-	-	-	-	C Venturin et al. 2017 [16]
CD	24	Until 30th weeks of gestation	Full-term, healthy	0.3	4.1	-	-	Klenske et al. 2019 [12]
CD	35	Until 33rd weeks of gestation	Full-term, healthy	4.3	8.0	Normal	-	Rowan et al. 2018 [13]

agents are administered during the late gestation period. Table 2 shows detailed conditions of the newborn babies. All babies were born by cesarean delivery at full term without any complications, and there were no congenital abnormalities found in them (APGAR score at five minutes was 8 in all cases, within the normal range). Their mean birth weight was 3076 ± 262 g. The babies grew up regularly without any developmental disorders or susceptibility to infection by the age of six months.

Two of the 3 babies, in which their mothers received IFX after 30 weeks of gestation (cases 1-3), were detected a small amount of IFX in peripheral blood drawn at six months of age. Therefore, they received BCG after confirming blood IFX levels to be below the detection limit at nine months of age. All cases did not receive rotavirus vaccines that are normally recommended to start the first dose by six weeks of age. These results suggest that the administration of IFX in late gestation period affect neither the growth and development of the fetus nor the delivery course, but it may remain in baby's body for over six months.

UST treatment may not bring adverse events to pregnancy and delivery

Case 5 started UST treatment after her second bowel resection as a maintenance therapy that was 4 months before pregnancy. Clinical remission was maintained throughout the course of pregnancy as described above. The baby was born by cesarean delivery at 38 weeks and 0 days of gestation weighing 2596 g without complications (Table 2). The baby grew up and well-developed without any signs of susceptibility to infection up to six months of age. There are also case reports documenting UST use in pregnant CD patients up to late gestation period and the outcomes of their childbirth (Table 3)[11-13]. Any of these five cases, including our case 5, did not show unexpected adverse outcomes of pregnancy and child growth. These results suggest that UST treatment for pregnant CD patients may be safe and does not have adverse effect in embryogenesis, fetal growth, delivery, as well as the development of new born babies.

UST concentration is higher in cord blood than in maternal peripheral blood at delivery but may be cleared from the baby's bloodstream in six months if administered by 23 weeks of gestation

Pharmacokinetics of UST in mothers and their babies is still unclear. Therefore, we measured UST concentrations in maternal peripheral blood and cord blood at delivery and in the baby's blood at six months of age. We found in case 5 that the concentration of UST in cord blood was 756.5 ng/ml, which was higher than that in maternal blood (267.7 ng/ml) at delivery (Table 2). Nevertheless, we confirmed that UST in infant's peripheral blood was below the detection level at six months of age. Then the child received BCG without any adverse events. The trend of UST distributions in mother-fetus interactions was similar to the previous reports (Table 3). Therefore, the distribution of UST among mother's body, cord blood, and infants may not be equivalent.

Discussion

Pregnancy and childbirth are major life events for women and may raise many concerns by those who have chronic diseases such as CD. One of their major matters associates with medications; if their medications are safe for the baby and what can be other options if they have to discontinue the medication. In this case series, we describe that the treatment of pregnant CD patients with biologics in the late gestation period does not adversely affect the course of pregnancy and delivery. However, IFX could remain in babi-

es' bloodstream for over six months if their mothers received IFX in the late gestation period. It is still uncertain whether blocking TNF-α in early life influences one's development of the immune system and increases future susceptibility to infections or malignancies that has been associated with this class of drugs[14]. Use of UST for pregnant patients with CD also appears to be safe and effective in most cases[11-13]. A recent cohort study has shown that the rates of prematurity, spontaneous abortion, congenital malformations, and maternal complications in the pregnant IBD patients on UST or Vedolizumab are similar to that in individuals on anti-TNF-α agents[15]. Our case had kept her CD quiescent throughout pregnancy by using UST and successfully delivered a healthy baby. Because there has been a report shown a pregnant CD patient who received UST experienced a miscarriage despite her CD had been gotten into clinical remission, accumulation of more clinical data would be required to conclude the safe use of UST for pregnant CD patients[16]. The eldest child in our series is currently three years old and he has grown up without any physical or mental problems. Because pregnancy may not be safely carried in active CD patients and the increased risk of miscarriage and preterm or low-birthweight delivery have much more health impact on them and their babies as well, one can say that keeping their CD activity quiescent by the administration of biologics even in their late gestation period would be beneficial at this point. Our results support this idea and provide further information for safer management of pregnancy and their newborn babies in patients with active CD.

The distribution of exogenously administered IgG_1 among the mother's body, fetus, and umbilical cord involves multiple metabolic factors and maturation of placenta[17]. Studies have shown that the concentration of biologic agents in umbilical cords correlates with the timing of the final doses before delivery[4,18]. In general, mother's IgG is transmitted to the fetus mainly after the 28th week of gestation and fetal blood IgG concentrations exceed maternal levels up to 30% by full term[19]. Therefore, it is likely that a substantial amount of the biologic agent administered to pregnant patients after late gestation period may be transferred to the fetus. Several reports have shown a significant difference in the concentrations of anti-TNF-α agents in cord blood and newborn babies between pregnant patients with CD who stopped the treatment before and after 30 weeks of gestation[4,20]. In our cases, there were three patients who received IFX after 30 weeks of gestation. Two of the three babies from these patients were detected IFX in their blood at six months after birth, that had become undetectable by the age of nine months. We measured maternal serum levels of CRP and albumin at delivery as they might affect trough levels of IFX in mothers but no associations were seen between these markers and the positivity of IFX in babies' blood at six months old. Because clearance and half-life of IFX in both pregnant patients and newborn babies differ from non-pregnant CD patients[4,6], we may not directly use the known predictive markers of IFX trough levels in CD patients to know the rate of placental transfer of IFX to the babies. Therefore, currently available predictive factors of pathologically significant placental transfer of IFX from mothers to babies would be the timing of the last IFX dose; which is after 30 weeks of gestation.

It has been reported that exposure to biologics in the womb leads to neither serious infections nor developmental defects in newborn babies[21]. Along with the PIANO (Pregnancy in IBD and Neonatal Outcomes) registry, an ongoing prospective study in the United States, we have continuously monitored the children's health in this study and no particular health issues have been identified so far. Although the PIANO registry has indicated that UST and anti-TNF-α therapies during the third trimester of pregnancy does not increase the risk of general and vaccination-associated infections[3,9], our results show prolonged retention of IFX more than six months in babies whose mothers received IFX after 30 weeks of gestation. Other reports have also warned that live vaccines should be held up to one year unless the clearance of IFX in infants are confirmed because IFX may increase the risk of vaccination-associated infections[4]. While vaccination is an effective primary prevention strategy, adverse events, including vaccination-associated infections, may lead to serious morbidity and mortality in children exposed to biologics in utero and thus the risk and benefit of live vaccines for those children need to be carefully assessed[8,9,22,23].

The concomitant use of thiopurine with anti-TNF-α agents during pregnancy has been shown to increase the risk for infant infections 2.7 times during the first year[4,24]. One of our cases that detected IFX in blood at six months old was an infant whose mother was on AZA and received IFX until 32 weeks of gestation. AZA monotherapy in pregnant CD patients is known to have no associations to increased susceptibility to infections[25]. It is still unclear why the combination therapy with IFX plus AZA for pregnant CD patients leads to the increased risk of infant's infections because less than 5% of AZA will be transferred from mother to infant and that will be quickly inactivated by the baby's high metabolic activities[26,27]. In any case, these conflicting data maybe due to the metabolic complexity in mother-fetus interactions as well as the functional variability of the immune system in newborn babies.

Since controlling maternal disease activity should be prioritized in pregnant patients with CD[28], we want to highlight that physicians need to be confident to provide biologics for pregnant CD patients with this purpose. One thing we need to take into account is that biologics can be transferred to babies and retain over six months after birth. It is

likely that infant's trough levels of biologics (both IFX and UST) are much higher than that in mother's blood at birth and each half-lives of these biologics is much longer in infants than adults. While most guidelines recommend holding live vaccines up to six months for such babies[2,3], our data indicate that it may be safer to directly check serum concentration of the biologics before applying live vaccines to them. Because the key cytokines blocked by the biologics (TNF-α for IFX and IL-12/IL-23 for UST) play important roles in antigen presentation and development of antigen-specific immunity[29], there should be certain effects of biologics circulating in infant's body on vaccination-induced immune responses regardless of their biological significance. As the immune function of each individual vary per se, accumulating case reports of pregnant CD patients and their babies who are treated with biologics will eventually guide us to the best medication and appropriate follow-up strategies for pregnant CD patients and their children, respectively.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Minako Sako designed the study with Makiko Mine and executed data acquisition, analysis, and drafted the manuscript. Akira Sonoda analyzed main data and created the figures and tables. Naoki Yoshimura, Soh Okano, Maki Tezuka, Shingo Yamanishi, Koichi Hashimoto, Koichi Kobayashi, and Masakazu Takazoe managed patient enrollment and helped data collection. Masayuki Fukata oversaw entire project and interpreted data and drafted the manuscript. All of the authors have approved the contents of this paper and have agreed to the submission policies of Journal of the Anus, Rectum and Colon.

Approval by Institutional Review Board (IRB)

This study was approved by the Institutional Review Board (IRB) of Tokyo Yamate Medical Center (J-072).

Informed Consent

Informed consents were obtained from all the patients involved in this study.

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