Successful Treatment with Adalimumab for Intestinal Behcet’s Disease during Pregnancy

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Abstract

A 36-year-old Japanese woman with intestinal Behçet’s disease was admitted to our hospital due to a recurrent ileocecal ulcer. Because infliximab (IFX) showed secondary failure, IFX was switched to adalimumab (ADA). After the third injection of ADA, she was unexpectedly 4-weeks pregnant. ADA was continued until 20 gestational weeks. Remission of the disease activity was maintained during pregnancy, and the birth was uneventful. The ileocecal ulcer disappeared after her delivery. ADA was detected in the umbilical blood after 119 days from the last infusion. The placental transition and timing of neonatal vaccination should be considered in cases of pregnancy with TNF antibody therapy.

Key words: adalimumab, intestinal Behçet’s disease, pregnancy, placental transition

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Introduction

Behçet’s disease (BD) is chronic relapsing disease with recurrent oral aphthous ulcers, genital ulcers, and uveitis. Occasionally, BD also involves visceral organs such as the gastrointestinal, vascular and neurological systems (1). Intestinal BD can be a life-threatening manifestation due to gastrointestinal bleeding and perforation. Surgical treatment is often necessary for refractory intestinal BD, despite treatment with high doses of corticosteroids, sulfasalazine and immunosuppressants. Recently, the efficacy of the anti-TNFα monoclonal antibody (mAb) infliximab (IFX) has been reported (2, 3). In Japan, adalimumab (ADA) was approved as the first TNF inhibitor for intestinal BD in May 2013 (4). Anti-TNF mAbs can cross the placenta from the late stage of the second trimester of gestation (5). Case reports of treatment with TNF inhibitors during pregnancy have accumulated in patients with inflammatory bowel disease (IBD) (6). Nevertheless, the long-term safety has not been completely established, thus discontinuation of TNF inhibitors during pregnancy is desirable if at all possible. We herein present a patient with intestinal BD having an ileocecal ulcer for who continuation of ADA treatment during pregnancy had beneficial effects.

Case Report

In 2010, a 33-year-old Japanese woman presented with a low-grade fever, oral aphthous ulcer, genital ulcer, abdominal pain and hemorrhagic stool. She was diagnosed with intestinal BD according to the finding of an ileocecal ulcer on colonoscopy. She was treated with oral corticosteroid (prednisolone 40 mg/day) and mesalazine 1,500 mg/day. Her symptoms improved and prednisolone (PSL) was tapered to 13 mg/day. She carried her first baby in 2011. The disease worsened during pregnancy with continual prednisolone and mesalazine treatment, and she gave birth early at 32 gestational weeks. After delivery, she suffered a multiple compression fracture of the lumbar spine due to steroid-induced osteoporosis. In the previous year, she had been in good condition, taking oral PSL 15 mg/day, mesalazine 2,000 mg/day and azathioprine 50 mg/day. In 2013, at 36 years of age, the patient was referred to our hospital due to worsen-
ing abdominal pain and an oral aphthous ulcer without ocular symptoms. Laboratory data revealed an elevated white blood cell count (10,630/μL), but normal-range values for C-reactive protein, antinuclear antibody, antineutrophil cytoplasmic antibody, complement, interferon-gamma release (QuantiFERON® assay) and cytomegalovirus antigenemia (C7-HRP). Her HLA typing B51 was negative. On colonoscopy, a deep punched-out ulcer with clear margins was observed in the ileocecum (Fig. 1A). The histological examination revealed ulceration with infiltration of inflammatory cells including neutrophils. She was given three injections of IFX 5 mg/kg at 0, 2, and 6 weeks for the active ileocecal ulcer. Her abdominal pain initially improved, and PSL was tapered from 15 mg/day to 5 mg/day, however, this symptom relapsed after the third injection (Fig. 2). The ileocecal ulcer remained on colonoscopy at 12 weeks from the initiation of IFX (Fig. 1B). She was then switched from IFX to ADA, with subcutaneous injections of 160 mg, 80 mg, and 40 mg biweekly. Unexpectedly, 6 weeks after the initiation of ADA, she discovered she was 4-weeks pregnant. She agreed to the continuation of ADA treatment after informed consent. Her abdominal symptom disappeared gradually, leading to remission. ADA treatment was continued until the 20th gestational week and was subsequently stopped in consideration of the placental transition. She delivered the baby at 37 gestational weeks without any difficulties. On colonoscopy, the ileocecal ulcer disappeared at 10 weeks after delivery (Fig. 1C). Because a low level of ADA was detected
in the serum of the umbilical cord and fetus at birth (1,670 ng/mL and 1,660 ng/mL, respectively), the baby’s BCG vaccination was delayed until 6 months after birth. The patient had no recurrent episodes, and the baby has been growing without any troubles during the one-year follow-up.

**Discussion**

BD is a chronic systemic inflammatory disorder whose etiology has not been fully established. It has long been regarded as a Th1-type autoimmune disease due to its association with HLA-B51 (7). Intestinal BD is characterized by deep, round punched-out ulcers in the terminal ileum. The frequency of intestinal BD is more common in Japan (13-25%) than in Turkey (5%) (1). In the EULAR recommendation for BD, there is no evidenced-based treatment for the management of gastrointestinal involvement of BD (8). Immunosuppressive therapy such as corticosteroids, azathioprine and TNFα antagonists are used empirically in the treatment of intestinal BD. Recently, the efficacy of TNF inhibitors for not only ocular, but also gastrointestinal manifestations of BD has been reported (2, 3). In a consensus statement of an expert panel of Japanese gastroenterology and rheumatology specialists, anti-TNFα monoclonal antibodies (ADA and IFX) should be considered as both induction and maintenance therapies for intestinal BD (4). In the present case, intestinal BD relapsed while continuing prednisolone, mesalazine and azathioprine, and the administration of TNF inhibitors led to remission.

It is unclear whether the disease activity of BD worsens during pregnancy. In a systematic review of the literature, the course of BD was ameliorated or unchanged in most cases, however, the outcome of pregnancy in BD patients was poorer than that in healthy individuals (9). Unfortunately, it is difficult to predict the course for individual cases during pregnancy. It is important to follow such patients carefully. In patients with IBD, active disease at the time of conception has been associated with increased rates of preterm birth (10) and fetal loss (11), and disease flares during pregnancy have been associated with preterm birth and low birth weight (12). These findings indicate that control of the disease activity during the time of pregnancy is important. The present case had a risk of disease flare because the disease activity had worsened during the first pregnancy. Several systematic reviews and meta-analyses in woman with IBD provide support for azathioprine with minimal effect to the fetus (13, 14). To maintain remission of intestinal BD, continuation of azathioprine as well as ADA was necessary in the present case.

Over the course of pregnancy, IgG levels in the fetal circulation increase and exceed those in the maternal circulation at the end of gestation (15). Fc receptors on synctiotrophoblast cells bind IgG from the maternal circulation and transport it into the fetal circulation (5). The mechanism is referred to as active placental transport, and the placenta utilizes this mechanism to bind Fc receptors and IgG during pregnancy. Therefore, anti-TNF mAbs with an Fc fragment, such as IFX and ADA, are expected to be more easily transferred across the placental barrier than the PEGylated Fab fragment of an anti-TNF mAb without an Fc fragment, for instance, certolizumab pegol (CZP). Etanercept (ETA), a recombinant TNF receptor Fc fusion protein, is also considered to have a low placental transition due to its structure. Indeed, the concentration of CZP and ETA in infants and their cords were lower than that in the maternal serum during pregnancy (16, 17). On the other hand, concentrations of IFX and ADA were higher in infants at birth and their cords than in their mothers, and these drugs were detected in infants up to 6 months after birth (16). The concentration of ADA in the maternal serum was not examined in the present case. However, the ADA concentration of the infant and cord is expected to be higher than that of the maternal serum. The time dose to birth was 119 days in the present case. This is the longest case among previous cases in which the measurement of ADA in the umbilical blood has been performed.

There is no report that exposure to TNF inhibitors is toxic to the developing fetus (6). However, due to the limitations of available data and lack of controlled trials, there is not sufficient evidence to demonstrate the safety of the fetus exposed to TNF inhibitors during pregnancy. Moreover, the long-term safety of the infant is uncertain. If possible, discontinuation of the TNF inhibitor is desirable during pregnancy. If it appears to be necessary to use a TNF inhibitor to control the disease activity during mid and late pregnancy, then inoculations of live vaccine after birth pose a problem. It was reported that an infant born from a patient with Crohn’s disease and exposed to infliximab during pregnancy died due to disseminated BCG because of a live vaccine received at 3 months of age (18). Therefore, any infant exposed to anti-TNF mAb in the uterus should be protected from the administration of a live vaccine until at least 6 months from birth or until the drug disappears from the serum (19). In Japan, BCG is regularly used as a vaccine up to 12 months after birth. In the present case, because a small concentration of ADA was detected at birth, vaccination of the infant with a live vaccine was postponed until 6 months after birth. The vaccination of BCG had no adverse effect to the infant during the one-year follow-up.

We herein presented a patient with intestinal BD having an active ileocecal ulcer and treated with ADA during the first 20 weeks of pregnancy with no apparent consequence to the fetus. TNF inhibitors should be discontinued during pregnancy if the patient’s condition is stable. When it appears to be necessary to use a TNF mAb, the timing of vaccination with a live vaccine after birth should be considered according to the placental transition.

The authors state that they have no Conflict of Interest (COI).
References