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CASE REPORT

A case of planned pregnancy with an interruption in infliximab administration in a 27-year-old female patient with rheumatoid-factor-positive polyarthritis juvenile idiopathic arthritis which improved after restarting infliximab and methotrexate

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Abstract We report a 27-year-old case of juvenile idiopathic arthritis (JIA) having been stopped infliximab during pregnancy. She was safely treated by infliximab therapy with premedications for preventing infusin reactions after her delivery, and then improved in the same manner as when she had been treated with infliximab therapy before pregnancy. As a result, it remains unclear whether or not we can use infliximab to control disease activities during pregnancy. In addition, it is also important to clarify whether or not premedications should be used when resuming infliximab treatment in such patients after pregnancy. These problems still remain controversial. More definitive data are needed in order to allow rheumatologists to better select the optimal TNF-alpha inhibitor therapy when treating pregnant JIA patients.

Keywords Pregnancy · Infliximab · Juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disorder in childhood. A persistent destructive arthritis occurs in many patients with polyarticular course JIA. Over the past few years, tumor necrosis factor (TNF)-alpha-blocking agents have been increasingly used in the treatment of more severe refractory JIA and rheumatoid arthritis (RA), and a significant improvement in such patients has thus been observed [1, 2].

For reproductive age female patients with JIA, there are important questions about fetal safety if a woman becomes pregnant. However, there is limited information on fetal safety in pregnant patients with not only JIA [3] but also RA [4] who were treated with TNF-alpha-blocking agents.

We report here a female with rheumatoid-factor-positive polyarthritis JIA who improved after restarting treatment

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with infliximab and methotrexate, which had been discontinued during her planned pregnancy.

Case

A 27-year-old woman with a 14-year history of rheumatoid-factor-positive polyarticular course JIA presented 3 months before her first planned pregnancy. Previous combination therapy, which included bucillamine, cyclosporin A and methotrexate (MTX), had failed to control her disease. She had been treated with infliximab since November 2003 at 24 years of age. She received 200 mg of intravenous infliximab at weeks 0, 2 and 6 and every 8 weeks thereafter. At 40 weeks, she suffered an arthritis flare and the interval between the infusions of infliximab had to be shortened from 8 to 4 weeks. At 60 weeks, she showed a good response again and the interval was lengthened from 4 to 6 weeks. Exceptionally, at 82 weeks, the interval between infusions was shortened from 6 to 4 weeks because she was getting worse due to the stress of her honeymoon (Fig. 1). She consulted us regarding her desire to conceive a baby. At the time of presentation, she was taking 200 mg of infliximab every 4 weeks and oral 12.5 mg of MTX weekly. She had no active arthritis and her disease activity score 28 (DAS28) was 1.94. We therefore advised her to stop taking infliximab and MTX immediately.

She suffered an arthritis flare in the right knee joint 1 month after withdrawal of infliximab and MTX (Fig. 2). The flares were treated with oral predonisolone and twice intravascular dexamethasone palmitate injections before the pregnancy test was positive. Her DAS28 worsened, from 1.94 to 5.74, before she became pregnant. She had the last infliximab and MTX 4 months before a positive pregnancy test was obtained. She was advised to increase predonisolone from 10 to 15 mg. Her condition did not improve until 24 gestational weeks.

At gestational week 22, she was admitted because an ultrasound of the fetus showed severe intrauterine growth retardation. She had no maternal problems except for severe intrauterine growth retardation. The patients delivered a female baby weighing 982 g at gestational week 34 by Caesarean section. The baby was treated by intubation due to infant respiratory distress syndrome. However, the baby did not have any congenital malformations and thereafter developed steadily.

The patient was advised not to breast-feed. MTX was restarted 1 week after delivery and infliximab was restarted 4 weeks after delivery. The patient was pretreated with a combination of H1, H2 blockers and hydrocortisone. Cetirizine 10 mg per day and ranitidine 300 mg per day were given for 3 days and continued for 4 days after the infliximab infusion. Hydrocortisone 100 mg was infused before infliximab. We stopped hydrocortisone at the second infusion, ranitidine at the third infusion and cetirizine at the fourth infusion. The fourth infusion was continued safely without premedications. Her DAS 28 improved from 3.91 to 2.55 at the fourth infusion of restarted infliximab.

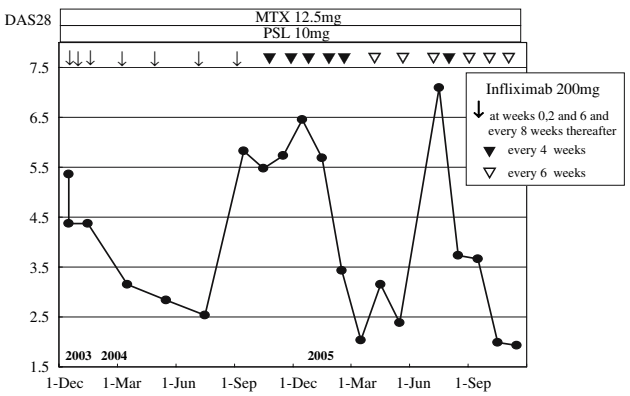

Fig. 1 The change of DAS28 before her planned pregnancy. She received 200 mg of intravenous infliximab at weeks 0, 2 and 6 and every 8 weeks thereafter. At 40 weeks, she suffered an arthritis flare and the interval between infusions of infliximab had to be shortened from 8 to 4 weeks. At 60 weeks, she obtained a good response again and the interval was lengthened from 4 to 6 weeks. Exceptionally, at 82 weeks, the interval between infusions was shortened from 6 to 4 weeks because her condition had worsened due to the stress of honeymoon

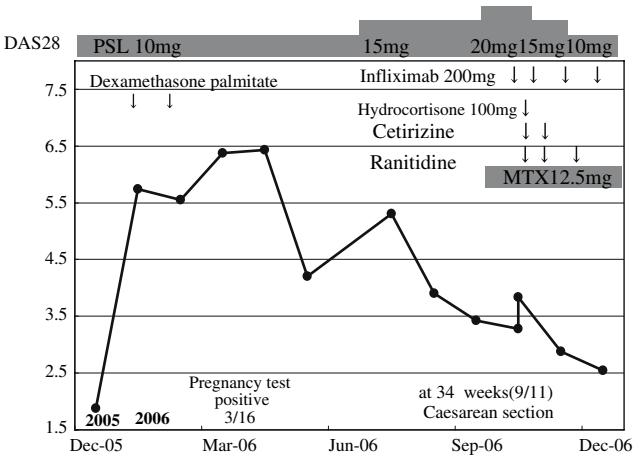

Fig. 2 The change of DAS28 after pregnancy and infliximab restarted. The flares after the withdrawal of infliximab and MTX were treated with twice intravascular dexamethasone palmitate injections before her pregnancy test was positive. Her DAS28 worsened, from 1.94 to 5.74, before she became pregnant. MTX was restarted 1 week after delivery and infliximab was restarted 4 weeks after delivery. The patient was pretreated with a combination of HI, H2 blockers and hydrocortisone. The fourth infusion was continued safely without premedications. Her DAS 28 improved from 3.91 to 2.55 at the fourth infusion of restarted infliximab

Discussion

We have described a female with JIA who improved after restarting infliximab and MTX, which had been stopped during her planned pregnancy.

She stopped taking infliximab and MTX when she decided she wanted to conceive. Lewden et al. [5] concluded that no strong teratogenic risk is associated with low-dose MTX provided that the drug is discontinued as early as possible in a pregnant woman. However, Lloyd et al. [6] reported that the exposure to MTX in pregnancy is associated with a roughly 25% risk of fetal malformation. Since the safety of MTX in pregnancy has not yet been sufficiently proven, it was decided to discontinue MTX immediately in order to avoid the risk of MTX.

The Food and Drug Administration (FDA) has classified infliximab as a drug with a category B pregnancy risk: no adverse pregnancy effects have been observed in animal studies, but there have been insufficient controlled human studies. Many women taking TNF-alpha inhibitors become pregnant [7] and a planned pregnancy case continued until the time pregnancy was recognized [8]. However, we discontinued infliximab at the same time we stopped MTX, because infliximab is more effective with MTX than without it and the incidence risk of human antichimeric antibody increased without MTX.

She flared 1 month after the withdrawal of infliximab and MTX. The flares were treated with oral predonisolone and twice intravascular dexamethasone palmitate injections before the pregnancy test was positive. Although numerous retrospective and prospective studies show that about 75% of patients experience an improvement of the disease during pregnancy, our patient did not show any improvement up until gestational week 24. The same case using infliximab before pregnancy was reported [8]. We presume that many cases, in which the patient had to use infliximab for the treatment of severe RA and JIA, did not improve during pregnancy.

Information Services compared pregnancy outcomes in 32 patients with RA exposed to etanercept or infliximab with the outcomes in 74 patients with RA not exposed to anti-TNF-alpha therapy, and with 49 nondisease controls. The rates of miscarriage and fetal malformation did not differ significantly among the three groups, but there was a significant increase in the rates of preterm delivery and low-birth-weight infants in all patients with RA in comparison to the controls [9]. Joven [10] reported 11 pregnancies in 10 women receiving anti-TNF-alpha therapy in Spain. Six patients received biologic treatment for RA, two for psoriatic arthritis and two for JIA. There were six live births without any complications, two therapeutic terminations, one miscarriage and two cases for which no outcome data were available. The above finding thus suggests that anti-TNF-alpha agents are not teratogenic. Our patients delivered a low-birth-weight girl without any malformation. The delivery of low-birth-weight might not be caused by infliximab and MTX because the drugs were stopped 3 months before her pregnancy test was positive. This may be because we did not control her disease activity during pregnancy. In a retrospective series of ten women with Crohn's disease who were intentionally exposed to infliximab throughout pregnancy, all pregnancies yielded live births with no congenital malformations [11]. If we had used infliximab throughout pregnancy and controlled her disease activity, we thus could have prevented the occurrence of low-birth-weight delivery.

However, the available TNF-alpha inhibitor constructs are based on an IgG1 constant region, and IgG1 is the most efficiently transported immunoglobulin subclass across the placenta [12]. Placental transport of IgG is poor in the first trimester and more efficient during the second and third trimesters. Most female patients receiving TNF-alpha therapy have been reported to stop taking such medication in the first trimester of pregnancy, because there are scant data on the outcome of exposure to TNF-alpha inhibitors in the second and third trimesters of pregnancy [4, 8, 9]. It still remains controversial whether we should use infliximab to control disease activities for patients exposed to infliximab or whether we should not use infliximab because the safety of infliximab throughout pregnancy has not yet been sufficiently proven.

Methotrexate was restarted 1 week after delivery and infliximab was restarted 1 month after delivery. We considered whether we would switch from infliximab to etanercept or restart infliximab. Unfortunately, not all patients respond to etanercept switching after the cessation of infliximab treatment (approximately 60–70%) [13], and she had stopped infliximab due to her pregnancy and not due to an insufficient effect. We therefore decided to restart infliximab after her baby was safely delivered.

The incidence of infusion reactions to infliximab is low (approximately 5%) [14]. However, previous treatment with infliximab has been reported to be a risk factor for a severe infusion reaction in RA patients who are undergoing a new course of therapy with this agent after a lengthy interval [15]. However, Cheifetz [14] reported all seven patients who experienced an initial mild or moderate acute reaction were able to receive additional infusions with a prophylaxis protocol. Four patients experienced severe acute reactions. Three patients were retreated, two patients had no further problems, whereas one patient had a second severe acute reaction that rapidly resolved with treatment. We therefore presume that pretreatments can prevent a severe infusion reaction at restarting infliximab. We restarted infliximab and pretreated the patient with a combination of HI, H2 blockers and hydrocortisone. We

thereafter gradually stopped such premedication. The patient demonstrated no infusion reactions. However, it remains unclear whether premedication is needed when infliximab is restarted.

We have herein reported a case in which infliximab was safely resumed, after having been stopped during pregnancy, and the patient improved as with the previous infliximab therapy. It is interesting to clarify that severe JIA patients requiring the use of infliximab and methotrexate can have a baby. However, whether or not we should use infliximab to control the disease activities during pregnancy and whether premedication is needed when infliximab will be restarted remains unclear. As the treatment paradigms for JIA become more aggressive, more definitive data are needed to guide rheumatologists in managing TNF-alpha inhibitor therapy in pregnant patients.

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