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ORIGINAL ARTICLE

Effect of biologic disease-modifying anti-rheumatic drugs for patients with rheumatoid arthritis who hope to become mothers

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Abstract

Objectives We examined the effect of biologic disease-modifying anti-rheumatic drugs on the time to pregnancy in patients with rheumatoid arthritis who hope to become mothers. Additionally, we evaluated adverse pregnancy outcomes and risk factors of these drugs.

Method We retrospectively investigated 25 pregnancies of 19 patients who were taking disease-modifying anti-rheumatic drugs. In 15 pregnancies, patients continued biologic disease-modifying anti-rheumatic drugs until conception (group A). In 10 pregnancies, patients discontinued biologic disease-modifying anti-rheumatic drugs and conventional synthetic disease-modifying anti-rheumatic drugs at the time of planning to conceive (group B). We used tumor necrosis factor inhibitors (certolizumab pegol and etanercept) for group A patients.

Results The mean time to pregnancy was shorter in group A than in group B (5.9 ± 3.8 vs 11.0 ± 6.5 months, $P = 0.04$). The mean birth weight of newborns was lighter in group B than in group A (2446.5 ± 352.4 vs 2969.4 ± 459.9 g, $P = 0.007$). There were no significant differences in the rates of preterm birth, light-for-date, and premature rupture of the membranes between the groups. In patients with preterm birth or light-for-date newborns, the mean dose of corticosteroids during pregnancy was significantly higher compared with that in those with full-term birth or non-light-for-date newborns ($P = 0.02$, $P < 0.01$, respectively).

Conclusions In patients with rheumatoid arthritis who hope to conceive, continuing biologic disease-modifying anti-rheumatic drugs at the time of conception could shorten the time to pregnancy. Using biologic disease-modifying anti-rheumatic drugs before pregnancy does not affect abortion, preterm birth, light-for-date, and premature rupture of the membranes.

Keywords Biologic disease-modifying anti-rheumatic drugs · Conception · Light-for-date · Preterm birth · Rheumatoid arthritis · Time to pregnancy

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects women of childbearing age. Recently, progression of a treatment strategy using biologic disease-modifying anti-rheumatic drugs (bDMARDs) has considerably improved the prognosis of RA, and more patients with RA can have children. However, becoming mothers is more difficult for women with RA than for women without RA. A longitudinal, observational study of women with RA showed that, among women who expressed interest in having more children, 55% reported having fewer children than desired [1]. This previous study also showed that approximately 25% of women with RA who were diagnosed at a childbearing age experienced fertility problems, but there was no difference in the number of spontaneous abortions between women with and without RA. Jawaheer et al. reported that women with RA were more likely to have been treated for infertility and had a longer time to pregnancy than women without RA from the time of starting to attempt conception [2]. In a prospective cohort

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from the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, high disease activity (evaluated by the Disease Activity Score in 28 joints) resulted in a longer time to achieving conception [3]. Other risk factors for subfertility were shown to be age, nulliparity, and use of non-steroidal anti-inflammatory drugs or corticosteroids (prednisone > 7.5 mg).

Several studies have shown an increased risk for preterm birth or low birth weight in women with RA [4–10]. Additionally, a high disease activity of RA during pregnancy is associated with an increased risk of adverse pregnancy outcomes, including abortion, preterm birth, and low birth weight [4–6]. According to these issues for women of childbearing age with RA, achieving disease control is important for achieving motherhood. Pregnancy-compatible anti-rheumatic drugs are required to control disease activity before and during pregnancy. Tumor necrosis factor (TNF) inhibitors provide an effective therapeutic option for RA. The updated British Society for Rheumatology guidelines and European League Against Rheumatism recommendation provide advice on the use of TNF inhibitors in pregnancy [11, 12]. Recently, a meta-analysis showed that TNF inhibitors did not increase the rate of pregnancy-related complications [13]. Moreover, previous reports have shown that TNF inhibitors, especially adalimumab, combined with or without immunoglobulin, improve the outcome of infertile treatment [14–16]. However, there are limited data on the effect of TNF inhibitors on infertility in patients with RA.

Therefore, we examined whether TNF inhibitors shorten the time to pregnancy in patients with RA who hope to conceive and whether they affect adverse pregnancy outcomes (e.g., spontaneous abortion, preterm birth, light-for-date [LFD], and premature rupture of the membranes).

Materials and methods

Patients and data collection

We collected data that were obtained from medical records of patients with RA who were treated at Kagawa University Hospital between November 2007 and May 2018. All patients with RA who were enrolled in this study fulfilled the 1987 revised criteria of the American College of Rheumatology. We included 25 pregnancies complicated by RA, which could be managed from preconception counseling to pregnancy and delivery, in our institution. We categorized patients with RA who became mothers into two groups. Patients in group A continued TNF inhibitors (certolizumab pegol [CZP] and etanercept [ETN]) at preconception counseling until conception which meant until the confirmation of pregnancy. Patients in group B discontinued all bDMARDs and conventional synthetic DMARDs (csDMARDs; e.g., methotrexate and salazosulfapyridine) at preconception counseling. We investigated clinical features (age at conception, disease duration, and the rate of primiparity), the time to pregnancy (time from preconception counseling [starting to attempt fertilization] to becoming pregnant), the disease activity of RA, therapeutic agent use before and during pregnancy, and pregnancy outcomes (spontaneous abortion, gestational weeks at delivery, preterm birth, birth weight, LFD, and premature rupture of the membranes). LFD was defined as birth weight of the newborn lower than the 10th percentile. All data were collected from medical records. Disease activity scores were calculated by using the Simplified Disease Activity Index (SDAI). This study was approved by the Institutional Review Board of Kagawa University Hospital.

Statistical analysis

Values are shown as mean ± SD and number (percentage). Descriptive statistics of the two groups were compared using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. We also assessed the univariate relationships between adverse pregnancy outcomes (spontaneous abortion, preterm birth, LFD, and premature rupture of the membranes) and the following variables: age at conception, disease duration, SDAI, and treatment before and during pregnancy. A two-sided P value of < 0.05 was considered significant. All analyses were conducted using JMP for Mac, version 13.0.0 (SAS Institute, Tokyo, Japan).

Results

Patients' clinical background

A total of 25 pregnancies in 19 patients with RA were analyzed in our study. Six patients experienced two times of conception in our institution. The patients' characteristics are shown in Table 1. RA treatment with biologics using CZP (9 cases) and ETN (6 cases) were continued for group A patients until the time of conception. In one patient, CZP was continued at the second trimester. However, in the other patients, bDMARDs were discontinued at the time of conception. The mean gestational week when bDMARDs were discontinued was 6.6 ± 3.2 weeks. The mean age at conception and the rate of primiparity were not significantly different between the two groups. Additionally, there was no significant difference in the SDAI score at the time of planning for pregnancy and conception between the two groups. Four cases in both groups were exacerbated during pregnancy, and the dose of corticosteroid needed to be increased.

Table 1 Patients' characteristics

Characteristics	Group A ($n = 15$)	Group B ($n = 10$)	P value
Mean age at conception (years)	35.0 ± 4.1	31.5 ± 3.9	0.05
Mean age at disease onset (years)	29.9 ± 6.3	26.7 ± 3.4	0.33
Mean disease duration (years)	5.4 ± 3.3	4.8 ± 2.4	0.93
Primiparity, *n* (%)	7 (46.7)	7 (70.0)	0.25
Mean score of SDAI			
Planning for pregnancy	4.7 ± 5.3	7.5 ± 5.5	0.29
At the time of conceiving	3.8 ± 4.0	3.9 ± 3.1	0.74
Corticosteroid			
Mean dose before conception (mg/day)	2.4 ± 2.7	5.0 ± 4.8	0.20
Use during pregnancy, *n* (%)	8 (53.3)	8 (80.0)	0.17
Mean dose during pregnancy (mg/day)	3.6 ± 4.4	6.6 ± 5.0	0.11
Increase in dose during pregnancy, *n* (%)	4 (26.7)	4 (40.0)	0.48

Pregnancy outcome

The mean time to pregnancy was significantly shorter in group A than in group B (5.9 ± 3.8 vs 11.0 ± 6.5 months, $P = 0.04$) (Fig. 1). Table 2 shows the adverse pregnancy outcomes. There were no significant differences in the rates of abortion, preterm birth, LFD, and premature rupture of the membranes between the two groups. The mean birth weight of newborns in group B was significantly lighter than that in group A (2466.5 ± 352.4 vs 2969.4 ± 459.9 g, $P = 0.007$) (Fig. 2). However, the mean gestational week at delivery was not significantly different between groups A and B (38.6 ± 1.2 vs 38.1 ± 1.4 weeks, $P = 0.38$). There was no case of neonatal infection or malformation in each group.

Risk factors for adverse pregnancy outcomes

In the case of preterm birth, the mean corticosteroid dose during pregnancy was significantly higher than that in the other patients ($P = 0.02$). However, there was no significant difference in the rate of bDMARD use between patients with preterm birth and those with full-term birth ($P = 0.85$). Similarly, in the case of LFD newborns, the mean corticosteroid dose during pregnancy was significantly higher than that in those without LFD newborns ($P < 0.01$). There was no significant difference in the rate of bDMARD use between patients with LFD newborns and those without LFD newborns ($P = 0.07$). In the cases of abortion and premature rupture of the membranes, there was no significant difference in the corticosteroid dose and the rate of bDMARD.

Discussion

In this retrospective study, we showed that continuing bDMARD treatment from planning for pregnancy to conception had the advantage of shortening the time to pregnancy, and there was no association between bDMARD use and adverse pregnancy outcomes. In addition, continuing bDMARD increased the birth weight of newborns and decreased the corticosteroid dose during pregnancy. However, the mean dose of corticosteroids during pregnancy was a risk factor for preterm birth and LFD.

Patients with RA who hope to become mothers have a longer waiting time to pregnancy compared with patients without RA [2]. The exact mechanism by which RA may influence fertility is unclear. A previous study reported that women with RA were not associated with reduced

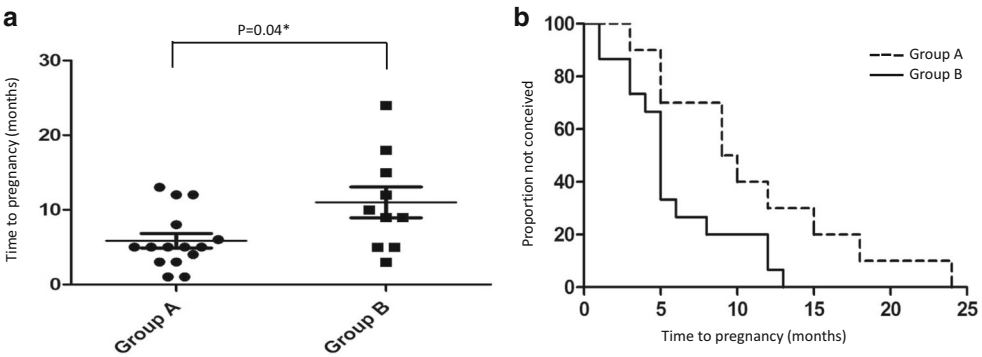

Fig. 1 **a** Comparison of the time to pregnancy between groups A and B with nonparametric analysis. **b** Survival curves showing the time to pregnancy in patients in groups A and B. Patients in group A could conceive for a significantly shorter time than those in group B ($P = 0.04$)

Table 2 Pregnancy outcome

Outcome	Group A ($n = 15$)	Group B ($n = 10$)	P value
Spontaneous abortion, n (%)	2 (13.3)	0 (0.0)	0.23
Mean gestational week at delivery (weeks)	38.6 ± 1.1	38.1 ± 1.4	0.38
Preterm birth, n (%)	1 (7.7)	1 (10.0)	0.85
Mean birth weight of newborns (g)	2969.4 ± 459.9	2466.5 ± 352.4	0.007
Light-for-date, n (%)	2 (15.4)	5 (50.0)	0.07
Premature rupture of the membranes, n (%)	6 (46.2)	3 (30.0)	0.43

ovarian reserve as evaluated by anti-Mullerian hormone levels [17]. Additionally, the PARA study showed that older age, nulliparity, higher disease activity, corticosteroids (> 7.5 mg/day), and nonsteroidal anti-inflammatory drug use (cyclooxygenase-2 inhibitors) were related to a prolonged time to pregnancy [3]. This previous study indicated that there was no relationship between fertility problems and bDMARDs. Our study showed that continuing bDMARDs until the time of pregnancy resulted in a shorter time to pregnancy (5.9 ± 3.8 months) than discontinuing bDMARDs and csDMARDs at the time of planning to conception (11.0 ± 6.5 months). Therefore, continuing bDMARD treatment had an advantage of subfertility in patients with RA. There was no significant difference in disease activity at the time of planning for conception and becoming pregnant between the two groups in our study. This finding indicated that a longer time to pregnancy in the group with discontinuation of bDMARDs and csDMARDs (group B) was not affected by high disease activity. Additionally, there was no significant difference in the rate of primiparity between the two groups. The time to pregnancy was not affected by gravidity in our study.

This is the first report to show that bDMARDs have a good effect on conception in patients with RA. The reason why bDMARD use can shorten the time to pregnancy remains unclear. However, previous reports have shown that TNF inhibitors improve the outcome of infertile treatment [14–16]. Hill et al. first reported a shift towards a Th1 cytokine bias in women with recurrent pregnancy loss in activation of peripheral blood lymphocytes with a trophoblast cell line [18]. A Th1/Th2 shift in the cytokine profile from Th2 to Th1 predominance might play a significant role in recurrent spontaneous abortion and implantation failure [19]. Therefore, therapeutic intervention limiting Th1 cytokines, including TNF-α, may shift the Th1/Th2 balance away from Th1 to Th2 predominance. TNF inhibitors have a positive effect on an infertile outcome by inhibiting production of TNF-α and improving Th1/Th2 balance [14–16]. We believe that bDMARDs might have affected the time to pregnancy with these Th1/Th2 paradigm shifts in our study.

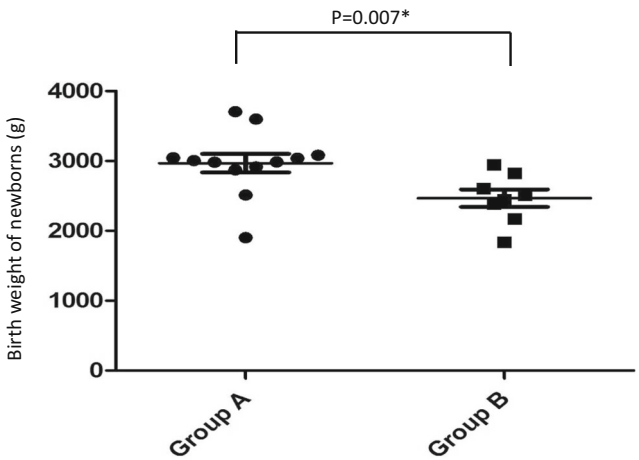

Fig. 2 Comparison of birth weight of newborns between groups A and B. The birth weight of newborns in group A was significantly lighter than that of those in group B

Our study also showed that the mean birth weight of newborns in the group with discontinuation of bDMARDs and csDMARDs (group B) at the time of hoping to conceive was significantly lighter than that in the group with continuation of bDMARDs until the time of pregnancy (group A). Additionally, there were no associations of abortion, preterm birth, LFD, and premature rupture of the membranes between the two groups. A recent meta-analysis that compared the pregnancy outcome between TNF inhibitor users and non-users showed that TNF inhibitors did not increase the rates of pregnancy-related complications [13]. In the Organization of Teratology Information Specialists (OTIS) study, preterm birth and birth weight at full term were the same between TNF inhibitor users and non-users [5]. In our study, CZP was used in nine pregnancies. Mariette et al. showed that CZP plasma levels of neonates born from mothers who were treated with CZP were undetectable at birth [20]. CZP was also reported not to increase the risk of malformation and pregnancy loss [21]. CZP treatment can be continued throughout pregnancy if considered necessary to control disease activity [20, 21].

In our study, the mean dose of corticosteroids during pregnancy in the group that discontinued bDMARDs and csDMARDs (group B) was higher than that in the group that continued bDMARDs at the time of conception (group A).

Additionally, the mean dose of corticosteroids during pregnancy was investigated as a risk factor for preterm birth and LFD. In the PARA study, gestational age at delivery was significantly lower in women who were taking prednisone ($P < 0.001$, 38.8 vs 39.9 weeks in women not taking prednisone), and this resulted in a lower birth weight in multiple linear regression analysis [4]. Women with RA who were treated with prednisone were also more likely to deliver before 37 weeks than those who were not treated with prednisone ($P = 0.004$) [4]. Other studies also showed higher rates of prematurity in women who were treated with corticosteroids during pregnancy [22, 23]. Our study showed that continuing bDMARDs at the time of conception resulted in a low dose of corticosteroid during pregnancy. This might have contributed to a decrease in the rates of preterm birth and LFD.

Our study has some limitations. First, there was a small number of outcome events, especially spontaneous abortion and preterm birth, because of the small number of patients, which might have resulted in low statistical power. Second, because this study was retrospective, we could not fully exclude selection or information bias, and some patients lacked data, such as the SDAI or disease duration, which might become less accurate. Third, this study was only conducted at our institution. Therefore, we may have included patients with a relatively high disease activity and high risk.

In conclusion, patients with RA should continue bDMARDs at the time of pregnancy, and these drugs have the advantage of shortening the time of pregnancy, increasing the birth weight of newborns, and decreasing the dose of corticosteroid during pregnancy. Using bDMARDs before pregnancy does not affect the rates of abortion, preterm birth, LFD, and premature rupture of the membranes.

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Compliance with ethical standards

Disclosures None.

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