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Disease Activity in Pregnant and Postpartum Women With Multiple Sclerosis Receiving Ocrelizumab or Other Disease-Modifying Therapies

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Abstract

Background and Objectives

Women with multiple sclerosis (MS) are at risk of disease reactivation in the early postpartum period. Ocrelizumab (OCR) is an anti-CD20 therapy highly effective at reducing MS disease activity. Data remain limited regarding use of disease-modifying therapies (DMTs), including OCR, and disease activity during peripregnancy periods.

Methods

We performed a retrospective cohort study using data from the MSBase Registry including pregnancies conceived after December 31, 2010, from women aged 18 years and older, with relapsing-remitting MS or clinically isolated syndrome. Women were classified by pre-conception exposure to DMTs, including OCR, rituximab (RTX), natalizumab (NAT), stratified into active (NAT-A; continued ≥28 weeks of gestation, restarted ≤1 month post-partum) or conservative (NAT-C; continued ≤4 weeks of gestation, restarted >1 month

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MSBase Study Group coinvestigators are listed in the appendix at the end of the article.

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Glossary

ARRs = annualized relapse rates; **CIS** = clinically isolated syndrome; **DMF** = dimethyl fumarate; **DMTs** = disease-modifying therapies; **EDSS** = Expanded Disability Status Scale; **IQR** = interquartile range; **MS** = multiple sclerosis; **NAT** = natalizumab; **OCR** = ocrelizumab; **RRMS** = relapsing-remitting MS; **RTX** = rituximab.

postpartum) strategies, dimethyl fumarate (DMF) or low-efficacy DMTs (interferon-beta, glatiramer acetate). Annualized relapse rates (ARRs) were calculated for 12-month prepregnancy, pregnancy, and 6-month postpartum periods.

Results

A total of 2,009 live births from 1,744 women were analyzed, including 73 live births from 69 women treated with preconception OCR. For OCR, no within-pregnancy relapse was observed and 3 women (4.1%) experienced 1 relapse in the postpartum period (ARR 0.09 [95% CI 0.02–0.27]). For NAT-A, 3 (3.7%) of 82 women relapsed during pregnancy (0.05 [0.01–0.15]) and 4 (4.9%) relapsed during postpartum (0.10 [0.03–0.26]). However, for NAT-C, 13 (15.9%) of 82 women relapsed within pregnancy (0.32 [0.20–0.51]) and 25 (30.5%) relapsed during postpartum (0.74 [0.50–1.06]). In the low-efficacy DMT group, 101 (7.6%) of 1,329 women experienced within-pregnancy relapse (0.12 [0.10–0.14]), followed by an increase in postpartum relapse activity with 234 women (17.6%) relapsing (0.43 [0.38–0.48]). This was similarly seen in the DMF group with 13 (7.9%) of 164 women experiencing within-pregnancy relapse (0.12 [0.06–0.20]) and 25 (15.2%) of 164 relapsing postpartum (0.39 [0.26–0.57]). Our RTX cohort had 0 of 24 women experiencing within-pregnancy relapse and 3 (12.5%) of 24 experiencing postpartum relapse.

Discussion

Women treated with OCR or NAT-A were observed to have low relapse rates during pregnancy and postpartum. NAT-C was associated with increased risk of relapses. There was no within-pregnancy relapse in our RTX cohort, although we caution overinterpretation due to our sample size. An effective DMT strategy with a favorable safety profile for the mother and infant should be discussed and implemented well in advance of planning a family.

Classification of Evidence

This study provides Class III evidence that for women with relapsing-remitting MS or clinically isolated syndrome who become pregnant, ocrelizumab, rituximab, and natalizumab (continued ≥28 weeks of gestation and restarted ≤1 month postpartum) were associated with reduced risk of relapses, compared with other therapeutic strategies.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS and a common cause of neurologic disability in young adults, particularly prevalent in women, with onset typically occurring during childbearing years. Historical studies of peripregnancy relapse in women with MS on either no or low-efficacy disease-modifying therapy (DMT) showed reductions during pregnancy, followed by a spike in the early postpartum period.[1,2] Recent studies that have included women treated with higher efficacy DMTs such as natalizumab (NAT) and fingolimod have revealed increased probabilities of relapse during pregnancy and postpartum periods, particularly after preconception DMT cessation and before reinitiation of therapy after delivery.[3,4] In addition, women who have more active disease with higher relapse rates and disability before conception are also at elevated risk of postpartum disease reactivation.[3,5]

Ocrelizumab (OCR) is a humanized monoclonal antibody that targets the CD20 cell surface antigen and modulates the immunopathogenesis of MS by depleting B cells. Pivotal clinical trials showed that administration of OCR at a 24-weekly dosing interval leads to significant reductions in disease activity and slowing of disease progression compared with interferon-beta in patients with relapsing MS and placebo in patients with primary progressive MS.[6,7] OCR efficacy was sustained in the open-label extension phases of the pivotal trials with safety profile consistent with clinical trial findings and no new safety signal identified with prolonged treatment.[8,9]

While available data on pregnancy outcomes after maternal exposure to OCR are reassuring to date,[10] data on postpartum disease activity control have only recently emerged. Several studies have described OCR and rituximab (RTX), another anti-CD20 monoclonal antibody that is used off-label in the treatment of MS, use before conception as associated with low rates of disease activity throughout pregnancy and during the postpartum period.[11-16] The effect of OCR on disease reactivation during the pregnancy and postpartum periods relative to other DMTs remains unclear.

In the setting of multiple DMTs available at present, data to inform counseling and management of optimal maternal and infant outcomes in the context of family planning are

important. Pivotal trials typically exclude pregnant women, and therefore, insights from observational studies are required. In this study, we sought to investigate disease activity during pregnancy and postpartum, in women who used OCR or other DMTs with accepted strategies for their use before conception and in the context of family planning.[17]

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase Registry has ethical approval granted by the Alfred Health Human Research and Ethics Committee and approval or exemption by local ethics committees at participating centers according to applicable local laws and regulations. Participants provided written or verbal consents based on local regulations.

Study Population

We performed a multicenter retrospective cohort study using patient, treatment, and pregnancy data, which were prospectively ascertained, from the MSBase International Registry.[18] Participating sites, many of which are tertiary MS referral centers, agree to collect a minimum data set of patient sex, birthdate, MS onset date, clinic visit dates, Expanded Disability Status Scale (EDSS; a nonlinear ordinal disability scale, range 0–10) assessments, relapse, and treatment information. Data on pregnancy are collected through a harmonized set of variables including date of delivery or termination, although this was not part of the MSBase minimum data set. Start of pregnancy is defined as the recorded last menstrual period or calculated from the estimated delivery date based on ultrasound assessment during pregnancy.[19] Any patient with MS who attends a participating center and provides informed consent can be enrolled in the registry. Data are most often collected and entered during clinical visits and into MSBase-specific data entry systems.

Data from the MSBase Registry were extracted on July 1, 2023. We included women who were at least 18 years old and had a relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS) phenotype at the start of pregnancy. The following DMTs, which have strategies considered compatible with pregnancy planning, were included: OCR or RTX as last DMT before conception and NAT, dimethyl fumarate (DMF), and low-efficacy DMT (interferon-beta and glatiramer acetate) as last DMT used before conception and dosing within 1 year before the start of pregnancy. We elected to analyze OCR and RTX groups separately, despite both DMTs targeting CD20-expressing cells, because of differences and heterogeneity in dosing (particularly for RTX because of its off-label use) and nuanced differences in biological effect.[20] Pregnancies that were ongoing or with an unclear outcome were excluded. Women were followed up to 6 months after pregnancy end. Pregnancies conceived after December 31, 2010, were included, to represent a modern DMT-treated cohort. Pregnancy outcomes were grouped as either term (≥37 weeks) and preterm (<37 weeks) live births or those with early termination (elective abortions, miscarriages (<gestational week 20), stillbirths (≥gestational week 20), and ectopic pregnancies). Of the cohort included in this study, 933 (38.8%) of 2,405 pregnancies contributed to the data set of our previous study.[3]

For OCR, the number of 600-mg doses used before pregnancy was estimated based on a 6-monthly dosing interval. For NAT, different treatment strategies, including duration of use into pregnancy and timing of reinitiation after delivery, have been shown to be differentially associated with pregnancy and postpartum rebound relapse activity.[3,21] Therefore, we defined an active strategy of NAT use (NAT-A) as continuation into at least 28 weeks of gestation, followed by reinitiation within 1 month after delivery, and a conservative approach (NAT-C) as NAT cessation at or before 4 weeks of gestation, followed by reinitiation more than 1 month after delivery.

Study Outcome

Relapse was defined as onset of focal or multifocal neurologic symptoms or signs that last at least 24 hours in absence of fever or infection. Annualized relapse rates (ARRs) were calculated as the number of relapses divided by the total included time. For each preconception DMT group, ARR was calculated per 3-month period for the 1 year before pregnancy and 6-month postpartum periods, respectively, and for each trimester for the pregnancy period. For the 1-year prepregnancy period, time after the preconception DMT was started until pregnancy start was included for calculation of ARR; i.e., only relapses after DMT initiation ± cessation were considered for the analysis. For the 6-month postpartum period, time before DMT recommencement and time after recommencement of the preconception DMT were included.

Statistical Analysis

Summary statistics were used to describe cohort characteristics. The Kruskal-Wallis test and χ^2 test were used to compare baseline characteristics across groups. A 2-sided p value of <0.05 was considered significant. Analyses were performed in the R statistical environment version 4.3.1 with the tidyverse package.[22,23]

Data Availability

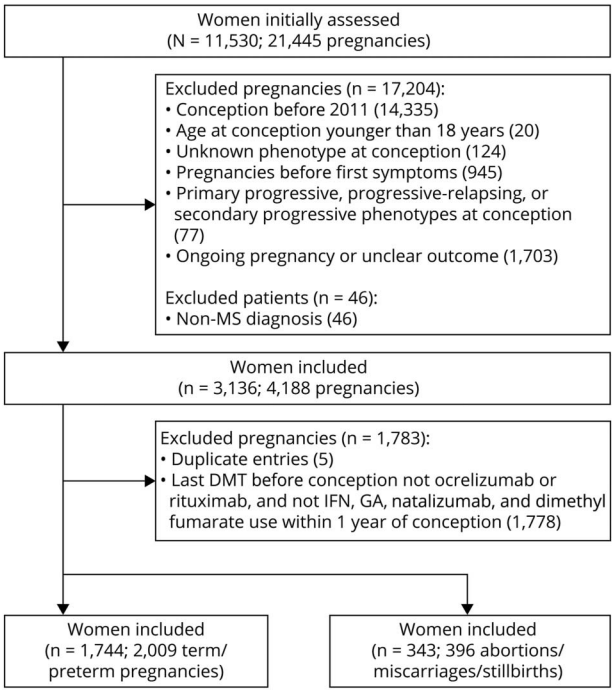
Patient-level data sharing is possible in principle but will require permissions/consent from each contributing data controller.

Results

Cohort Characteristics

We screened 21,445 pregnancies from 11,530 women and included 2,405 pregnancies from 1,921 women with RRMS or

Figure 1 Flowchart of Pregnancy and Patient Inclusion/Exclusion



CIS in the analyses. The median number of clinic visits recorded during pregnancy was 1 (interquartile range [IQR] 0–2) and during the 1-year postpartum period was 2 (IQR 1–3). Of these, 2,009 (83.5%) term/preterm live births from 1,744 women with preconception DMT exposure using OCR (n = 73), RTX (n = 24), NAT (n = 419), DMF (164), and low-efficacy DMT (n = 1,329) (Figure 1, Table 1) were included. Women receiving OCR were slightly older, had a higher level of disability at time of conception, and had been on their preconception DMT for a shorter duration compared with women who used other DMTs before conception (Table 1). Mean prepregnancy ARR was highest for the low-efficacy DMT group. The median number of OCR doses received before pregnancy was estimated to be 3 (IQR 2–4). In 21 pregnancies (28.8%), OCR was administered after the start of pregnancy (eFigure 1). For the 16 pregnancies with available within-pregnancy dose date, OCR administration occurred at median 32.5 days after pregnancy start (IQR 22.3–38.8). The proportion of DMT administration after the start of pregnancy (based on the last drug administration) was higher for other DMT groups; e.g., >74% of women using NAT before pregnancy had DMT exposure during pregnancy (eFigure 1). Of the NAT group, the proportion of pregnancies with NAT administration after the start of pregnancy increased over time (eFigure 2). Most of the women (n = 1,160, 57.7%) restarted the same category of DMT after delivery (Table 1; eFigure 3).

There were 396 pregnancies (16.5% of the 2,405 pregnancies included) that ended in early termination (elective abortion, miscarriage, stillbirth, or ectopic pregnancy) at a median of 8-week gestation (IQR 5.6–10.1 weeks) (eTable 1 describes characteristics of women with abortions, miscarriages, stillbirths, or ectopic pregnancies). Most of the early terminated pregnancies resulted in miscarriage (n = 243, 61.4%) or abortion (n = 144, 36.4%), rarely in ectopic pregnancy or stillbirths (n = 4, 1.0%, and n = 5, 1.3%, respectively). Preconception DMT exposure among early terminated pregnancies included 25 women (6.3%) treated with OCR (with an estimated median of 2 doses [IQR 2–3] administered before pregnancy), 1 (0.3%) with RTX, 87 (22.0%) with NAT, 30 (7.6%) with DMF, and 253 (63.9%) with low-efficacy DMT.

Preconception OCR and Other DMT Use and Relapse Rates Within Pregnancy and Postpartum Periods

For women with term/preterm live births, we plotted ARR summarized for each 3-month interval or pregnancy trimester by preconception DMT group (Figure 2, eFigure 4). In the OCR group, no relapse was observed during pregnancy. 3 women (4.1%) had 1 relapse in the 6-month postpartum period (ARR 0.09 [95% CI 0.02–0.27]). Relapse occurrence in relation to OCR infusion was scattered: one relapsed before OCR reinitiation, one on the day of OCR reinitiation, and another after OCR reinitiation. Clinical characteristics of these women are illustrated in Figure 3. For the low-efficacy DMT group, within-pregnancy relapse occurred in 101 pregnancies (7.6%) (ARR 0.12 [95% CI 0.10–0.14]) and was followed by an increase in the relapse rate after delivery with relapse occurrence in 234 women (17.6%) (ARR 0.43 [95% CI 0.38–0.48]). A similar postpartum increase in disease activity was seen in women who used DMF before pregnancy, with within-pregnancy relapse occurring in 13 women (7.9%) (ARR 0.12 [95% CI 0.06–0.20]) and postpartum relapse in 25 women (15.2%) (ARR 0.39 [95% CI 0.26–0.57]). For the overall NAT cohort, probabilities of relapse increased through pregnancy with relapse in 60 women (14.3%) (ARR 0.25 [95% CI 0.20–0.31]) and spiked in the postpartum period with relapse in 78 women (18.6%) (ARR 0.45 [95% CI 0.36–0.55]) (eFigure 4). In the NAT-A group, 3 women (3.7%) were observed to experience relapse during pregnancy (ARR 0.05 [95% CI 0.01–0.15]) and 4 women (4.9%) in the postpartum period (ARR 0.10 [95% CI 0.03–0.26]) (Figure 2). In the NAT-C group, 13 women (15.9%) relapsed in pregnancy (ARR 0.32 [95% CI 0.20–0.51]) and 25 women (30.5%) during the postpartum period (ARR 0.74 [95% CI 0.50–1.06]) (Figure 2). Owing to limited sample size limiting the ability to draw firm conclusions, we did not include our RTX cohort in our main analyses but have described relapse rates in our supplementary information (eFigure 5). In the RTX group, 3 (12.5%) of 24 women experienced postpartum relapse. The percentage of women with relapse by DMT group is summarized in eTable 2.

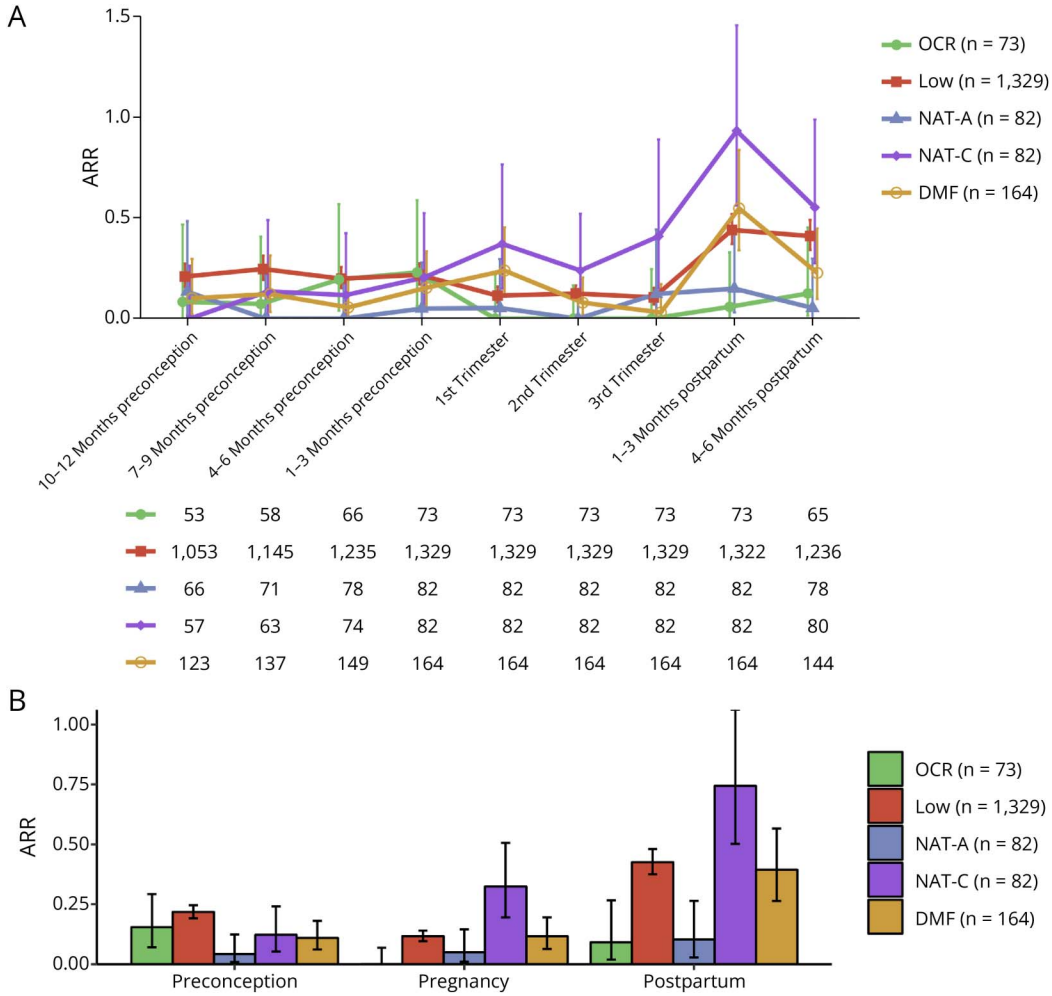
Of pregnancies with early termination, there was no within-pregnancy relapse among the women in the OCR group

Table Cohort Characteristics of Pregnancies Resulting in Live Births

					Preconception DMT			
	OCR (n = 73)	RTX (n = 24)	NAT (n = 419)	NAT-A (n = 82)[a]	NAT-C (n = 82)[a]	DMF (n = 164)	Low (n = 1,329)	*p*[b]
Pregnancy duration, median (IQR), weeks	39.0 (38.0–40.0)	38.1 (36.7–38.8)	38.7 (36.7–40.0)	38.9 (37.6–39.8)	38.0 (35.5–39.1)	39.0 (37.6–40.0)	39.0 (37.3–40.0)	0.052
Age at start of pregnancy, median (IQR), y	33.8 (30.7–37.3)	33.3 (29.1–35.0)	31.5 (28.6–34.4)	32.5 (28.5–35.3)	31.9 (29.4–34.0)	31.4 (28.4–34.2)	31.5 (28.2–34.6)	0.005
Time from first symptoms to start of pregnancy, median (IQR), y	7.10 (3.90–10.5)	6.16 (4.24–9.96)	7.41 (4.21–11.7)	7.59 (4.01–11.9)	8.59 (5.27–12.6)	5.70 (2.96–9.18)	5.83 (3.25–9.51)	<0.001
DMT used before, median (IQR), n	1 (0,2)	1 (0,2)	1 (1,2)	1 (0,2)	2 (1,2)	1 (0,2)	0 (0,1)	<0.001
EDSS score at start of pregnancy, n (%)[c]								<0.001
<2	25 (34.2)	12 (50)	198 (47.3)	39 (47.6)	41 (50.0)	95 (57.9)	674 (50.8)	
≥2	28 (38.4)	7 (29.2)	122 (29.1)	21 (25.6)	24 (29.3)	28 (17.1)	213 (16.0)	
Missing	20 (27.4)	5 (20.8)	99 (23.6)	22 (26.8)	17 (20.7)	41 (25.0)	441 (33.2)	
EDSS score at start of pregnancy, median (IQR)[c]	2 (1,2.5)	1.5 (0.5–2)	1.5 (1,2)	1 (0,2)	1.5 (1,2)	1 (1,1.5)	1 (0,1.5)	<0.001
Range	0,5	0,6	0,6	0,3	0,6	0,6	0,6.5	
ARR in 1 y before pregnancy, mean (SD)	0.14 (0.53)	0.13 (0.45)	0.11 (0.48)	0.05 (0.25)	0.11 (0.38)	0.20 (1.06)	0.24 (0.72)	<0.001
DMT prepregnancy duration, median (IQR), mo	9.95 (5.82–18.1)	16.7 (9.27–24.8)	18.1 (9.10–32.0)	24.8 (9.91–38.2)	16.0 (6.22–30.4)	14.1 (8.07–24.8)	23.5 (10.7–44.8)	<0.001
DMT washout, median (IQR), mo	1.87 (0–4.76)	3.43 (0.74–5.03)[d]	0 (0–0)	—	—	0 (0–1.32)	0 (0–0.821)	<0.001
DMT duration into pregnancy, median (IQR), mo	0 (0–0.460)	0 (0–0)[d]	0.89 (0–6.42)	—	—	0.21 (0–1.13)	0.49 (0–1.35)	<0.001
DMT initiated after delivery, n (%)[e]								
Ocrelizumab	43 (58.9)	1 (4.2)	12 (2.9)	0	0	2 (1.2)	1 (0.1)	
Natalizumab	2 (2.7)	0	304 (72.6)	82 (100)	82 (100)	6 (3.7)	18 (1.4)	
Dimethyl fumarate	0	0	3 (0.7)	0	0	76 (46.3)	25 (1.9)	
Low[f]	1 (1.4)	1 (4.2)	9 (2.1)	0	0	9 (5.5)	719 (54.1)	
Sphingosine-1-phosphate modulator[g]	1 (1.4)	0	14 (3.3)	0	0	4 (2.4)	38 (2.9)	
Rituximab	0	18 (75)	2 (0.5)	0	0	0	1 (0.1)	
Ofatumumab	2 (2.7)	1 (4.2)	1 (0.2)	0	0	1 (0.6)	0	
Alemtuzumab	0	0	9 (2.1)	0	0	0	1 (0.1)	
Cladribine	0	0	3 (0.7)	0	0	0	1 (0.1)	
None	24 (32.9)	3 (12.5)	62 (14.8)	0	0	66 (40.2)	525 (39.5)	
Time to DMT initiation after delivery, median (IQR), mo[h]	1.41 (0.49–3.02)	1.63 (0.77–1.91)[d]	0.89 (0.10–2.30)	—	—	2.25 (0.49–4.39)	2.43 (0.44–5.03)	<0.001

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; NAT = natalizumab; OCR = ocrelizumab, RTX = rituximab.
[a] NAT-A (active natalizumab strategy of continuation to ≥28 weeks of gestation and reinitiation within 1 month after delivery) and NAT-C (conservative strategy of cessation ≤4 weeks of gestation and reinitiation more than 1 month after delivery) were subset from the overall natalizumab (NAT) cohort.
[b] Comparisons were between OCR, RTX, NAT, DMF, and low-efficacy DMT groups.
[c] Calculated from women with available EDSS scores closest to start of pregnancy (within 1 year).
[d] Data available for 16 of 24 women in the RTX cohort.
[e] In the 6-mo postpartum period.
[f] Low-efficacy DMT initiated in the postpartum period include interferon-beta, glatiramer acetate, teriflunomide, azathioprine, and mycophenolate.
[g] Sphingosine-1-phosphate modulators include fingolimod and siponimod.
[h] Women who initiated either preconception DMT or other DMTs.

Figure 2 Annualized Relapse Rates (ARRs) Before Pregnancy, During Pregnancy, and in the Postpartum Period for Term/Preterm Pregnancies by Preconception Disease-Modifying Therapy Group



(A) ARR was plotted for each 3-month interval. (B) ARR was summarized for the 1-year prepregnancy, pregnancy, and 6-month postpartum periods, respectively. Natalizumab (NAT) groups represent either an active (NAT-A) or conservative (NAT-C) strategy of use during and after pregnancy. Low-efficacy group refers to interferon-beta or glatiramer acetate preconception use. Error bars represent 95% confidence intervals. Table represents number of women with time included for each 3-month interval. DMF = dimethyl fumarate; NAT = natalizumab; OCR = ocrelizumab.

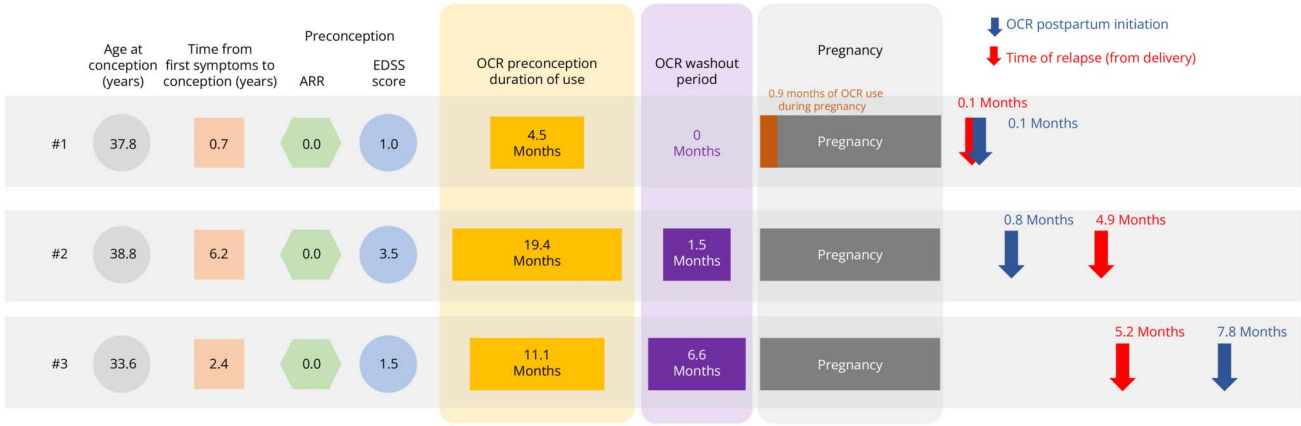
(Figure 4). In the postpregnancy period, ARR was lowest in the OCR group, with 2 women (8%) relapsing (ARR 0.16 [95% CI 0.02–0.59]). eTable 3 reports percentages of women with relapse by DMT group. This was highest in the low-efficacy group, in which 38 women (15%) relapsed (ARR 0.37 [95% CI 0.27–0.50]). There were 10 women (11.5%) who experienced relapse in the NAT group (ARR 0.27 [95% CI 0.14–0.49]) and 3 women (10%) in the DMF group (ARR 0.27 [95% CI 0.07–0.70]) after pregnancy. The 1 woman who used RTX before conception did not experience within-pregnancy or postpregnancy relapse.

Discussion

In this retrospective observational cohort study of women with relapse-onset MS, we observed no relapses during pregnancy and low relapse rates in the postpartum period in those who used OCR as the most recent DMT before conception. For women on NAT-A, low relapse rates during pregnancy and postpartum periods were recorded. Among women following a NAT-C strategy, or treated with DMF and other low-efficacy DMTs, relapse rates increased during pregnancy and/or postpartum periods. None of the women treated with RTX experienced within-pregnancy relapse, although our cohort size was limited for this group.

Among women in the OCR group, none had within-pregnancy relapse and only 3 experienced a postpartum relapse. Our data support the strategic use of OCR before conception as an effective option to maintain disease control during pregnancy and in the early postdelivery period, combined with a favorable safety profile for mothers and infants described by recently presented data.[10] 3 studies have investigated OCR and RTX use before pregnancy,[12,15,16] with several additional studies focusing on RTX.[11,13,14]

Figure 3 Characteristics of 3 Women Who Used Ocrelizumab (OCR) Before Conception and Experienced Postpartum Relapse



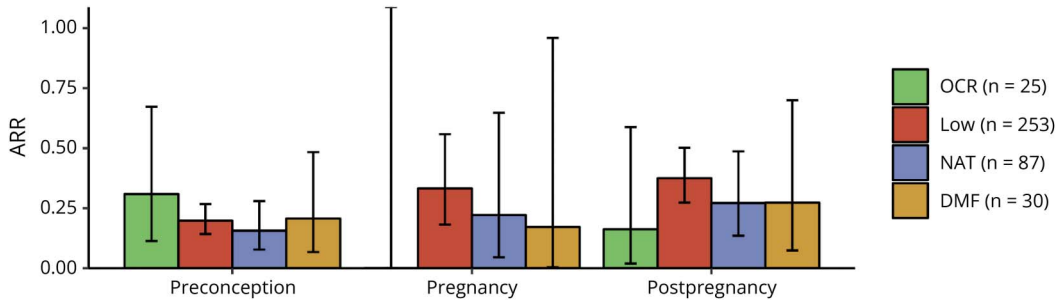
OCR use during pregnancy was based on the last administered dose. ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale.

Among these studies that included OCR, the number of included pregnancies ranged between 33 and 88, with the largest of these having 39 pregnancies (44%) with OCR used before and also including other neuroimmunologic diseases. These studies have described low rates of disease activity within pregnancy and generally also in the postpartum period (percentage with relapse ranged between 0 and 17%) among women treated with anti-CD20 therapy before pregnancy. Interpretations of our RTX cohort were limited by the small sample size, although the number of postpartum relapses after live births (3/24 [12.5%]) was consistent with one study.[12]

OCR has a sustained effect on peripheral B-cell depletion beyond its approved six-monthly dosing interval, as shown by a recent analysis of the phase II OCR extension trial data where MS disease control of at least 12–18 months was observed after 3 to 4 dosing cycles and while off treatment.[24,25] There are also data indicating a similarly prolonged efficacious effect after RTX dosing.[26] Considering our findings, planned use of OCR before conception may be a suitable strategy that can maintain maternal disease control during and after pregnancy while allowing for an administration-free pregnancy. Our findings support the efficacy of OCR in the context of pregnancy and align with expert guidelines that recommend strategic use of OCR for family planning.[17] Clinical studies are currently being conducted to gain further insights into efficacy and safety of using OCR during pregnancy.[27]

OCR labeling mandates a washout period of 6–12 months after the last infusion before trying to conceive.[28,29] However, recent guidelines and expert opinions recommend conception attempts from the next menstrual cycle after infusion[17] or as soon as after the most recent infusion,[30] with use of effective contraception earlier. This is based on minimal transplacental immunoglobulin transfer during the first trimester of gestation, drug pharmacokinetics, and the available reassuring pregnancy and infant outcome data from women who used

Figure 4 Annualized Relapse Rates (ARR) Before Pregnancy, During Pregnancy, and in the Postpartum Period for Abortions, Miscarriages, and Stillbirths by Preconception Disease-Modifying Therapy Group



Low-efficacy group refers to interferon-beta or glatiramer acetate preconception use. Error bars represent 95% confidence intervals. DMF = dimethyl fumarate; NAT = natalizumab; OCR = ocrelizumab.

OCR before conception.[10,12,31,32] The OCR cohort had a median time of 1.87 months between the start of pregnancy and prepregnancy infusion, with a quarter of included pregnancies having exposure to OCR mostly within the first trimester. Consistent patterns have been recently reported from the Roche Global Safety Database of women with MS exposed to OCR before or during pregnancy.[10] In this study, 60% of pregnancies were defined as exposed to OCR and most of these had dosing 0–3 months before the last menstrual period or in the first trimester of gestation. Data from this database did not identify a risk of adverse pregnancy or infant outcomes from in utero OCR exposure. Further studies are ongoing to better understand the benefit/risk of OCR exposure during pregnancy and lactation, including its effect on infant B-cell levels, placental/breastmilk transfer, and vaccine responses.[27]

Among our OCR and RTX cohorts, most of the women who restarted DMT did so within 3 months postpartum. While the RTX cohort was limited in its sample size, we observed low rates of postpartum relapse in the OCR group. In this study, we were not able to determine the optimal timing of anti-CD20 therapy restart after delivery. Previous cohorts of OCR or RTX use before pregnancy also reported median time to treatment reinitiation after delivery between 32 and 123 days.[12-16] The authors of several of these studies suggested that early reinitiation may be associated with reduced relapse risk, but their studies were not conclusive for this and so it remains open to future study.[12,15,16] Despite the risk of postpartum disease reactivation and current expert consensus for prompt resumption of DMT in the postpartum period to be considered particularly in women at highest relapse risk,[17] some tertiary centers suggest anti-CD20 therapy reinitiation 6–12 months postpartum because of concerns for cumulative risks of recurrent or serious infections and hypogammaglobulinemia.[14] A recent observational study outside the family planning context described RTX use, with maintenance dosing at 500 mg every 6–12 months in most of their cohort, and reported the incidence rate for serious infection among people with MS with a EDSS score ≤6 as 0.8 per 100 person-years.[33] Follow-up of 4,558 patients with relapsing MS receiving continuous treatment with 600-mg OCR every 6 months up to 10 years showed an incidence rate of 1.5 per 100 person-years for serious infection.[34] However, direct comparability between these studies and anti-CD20 therapy type and strategy is limited because of potential differences between cohorts. Further study is warranted to determine the optimal strategy of treatment in the postpartum period and potential safety signals in this population and guide treatment decisions that balance overall safety aspects and postpartum disease control.

Regarding the NAT strategy, we observed that the approach of NAT-A had lower ARR during and after pregnancy than the NAT-C group. The postpartum ARR seen for NAT-C was almost double that for the low-efficacy DMT group. Previous studies from our group and others have shown that NAT continuation into pregnancy reduced the risk of relapse within pregnancy, and that its cessation was associated with elevated risks of subsequent disease reactivation.[3,4,21,35,36] The latter may potentially augment the postpartum spike in disease activity. Over time, we observed an increasing proportion of pregnancies with exposure to NAT after conception, which likely reflected increased recognition for postcessation disease activation and emerging safety data of within-pregnancy NAT use,[35,37-39] although neonatal outcomes for this study cohort were incomplete and not reported. It is recognized that hematologic alterations of anemia and thrombocytopenia may occur in infants exposed to NAT in the third trimester of gestation. In an initial case series of NAT administration up to 36 weeks of gestation, 10 of 13 newborns had hematological abnormalities.[40] These abnormalities spontaneously resolved in most infants, and no specific treatment was required. Another case series of NAT administration during the third trimester (last infusion between 31 to 39 weeks of gestation) reported 4 of 15 newborns with hematological abnormalities, with no serious complication and 1 newborn receiving treatment with IV immunoglobulin and platelet transfusion.[37] All 4 of these newborns were associated with NAT infusion during pregnancy within 16 days of delivery. A recent study that included 121 NAT-exposed pregnancies (final infusion at median 31 weeks of gestation) with available neonatal blood cell counts found anemia or thrombocytopenia in 36.8% of neonates, most not requiring any specific treatment.[41] NAT administration beyond 30 weeks of gestation was associated with hematological abnormality in the neonate, although also associated with reduced maternal relapse and disability risks. While there are limited data so far on the effects of NAT continuation up to the early third trimester and pregnancy outcomes,[37,40,42] it emerges to be an accepted strategy in light of the importance of controlling disease activity and preventing clinically meaningful disability in the mother.[17,21,40,43]

Postpartum relapse rates were lowest in the OCR and NAT-A groups. A recent study compared OCR or RTX use in the 1 year before conception with a cohort that used NAT up to the first trimester of pregnancy before restarting after delivery.[16] The OCR/RTX group had increased odds of no disease activity during and after pregnancy, with this finding remaining significant when compared against the group who reinitiated NAT within 4 weeks of delivery. However, the early cessation of NAT in pregnancy may have contributed to further elevation of postpartum relapse risk in their cohort. Taking together the results of this and previous studies, the strategies of OCR administration before conception and no necessary dosing during pregnancy, or an active NAT strategy of continuation to 28–32 weeks of gestation with early reinitiation after delivery, are effective at minimizing pregnancy and postpartum disease activity risks. Although not investigated in this study, limited data are so far reassuring regarding OCR and NAT use and breastfeeding and infant safety,[31,44] with minimal drug transfer into breast milk and no safety signals identified for infants. This further strengthens the early initiation of these treatments because they can be considered

compatible with breastfeeding and recommended, given high risk of disease activity after delivery.[17,30] Concentrations and relative infant doses of these monoclonal antibodies in mature breast milk have been found to be low and at levels considered safe for breastfeeding.[15,44,45] Breastfeeding is encouraged, given its maternal and infant benefits.

In the cohort of women with early pregnancy terminations, we observed overall lower relapse rates in the 6-month postpregnancy period than in our cohort of women with live births. Potential factors for this observation are shorter gestational duration and lower rates of prolonged treatment discontinuation. Previous studies have reported increases in disease activity after abortion, miscarriage, and stillbirth and, therefore, suggest that clinicians and patients need to remain vigilant for disease reactivation in this early postpregnancy period.[3,46,47] The group of women treated with OCR before pregnancy had the lowest relapse rate after pregnancy, which is likely due to its high efficacy and durable response, although the small sample size limits interpretation of this finding.

Our study has several limitations. Data were contributed from specialty MS clinics, and our findings may not be generalizable to the broader MS population. We lacked sufficient MRI data to investigate imaging outcomes or corresponding fluid biomarkers such as serum neurofilament light chain. Infusion treatments such as OCR, RTX, and NAT are most commonly recorded in our data set as intervals rather than individual infusion dates, and so, we were not able to investigate the effect of total previous doses or dosing intervals on disease activity outcomes. Owing to its off-label use, RTX in MS has heterogeneous dose and dosing interval regimes, for which we had limited data in our data set. We were able to describe preconception OCR use in our cohort and contrast this with other DMT strategies, but given the limited number of postpartum relapses in the OCR cohort, it was not possible to investigate factors associated with postpartum relapse risk. In addition, we were unable to disentangle choice of postpartum DMT and optimal timing of postpartum DMT reinitiation strategies. Reinitiation of certain small-molecule DMTs such as sphingosine-1-phosphate receptor modulators and DMF is contraindicated for breastfeeding,[17] and many clinicians still advise a conservative approach with anti-CD20 therapy reinitiation if breastfeeding. In our real-world cohort, we did not have the granularity to determine why certain DMT were reinitiated over others; therefore, any conclusions drawn may have been subject to indication bias. To mitigate against this issue in this study, we included post-pregnancy follow-up time while the woman was on no treatment or if they restarted their preconception DMT and censored if they initiated a different DMT. Not all studied DMTs were available throughout the entirety of our defined epoch, which may also be a confounding factor. Baseline characteristics such as age, relapse rate, and disability likely influence the DMT strategy when trying to conceive. These are several of the complexities in the modeling for predictors of postpartum relapse, which we will address in our planned future work. The OCR cohort sample size was also not large enough for us to investigate postpartum disability progression as an outcome, based on the low rate we identified in our previous study.[3] It, therefore, remains to be determined to what extent the different treatment strategies, in the context of pregnancy, may affect long-term disability progression over several years after pregnancy. New MS DMTs have become available with limited evidence for use in pregnancy. Of particular interest here, we were unable to assess the use of ofatumumab, another newly approved anti-CD20 monoclonal antibody therapy, because of the recency of its approval and insufficient data available for analysis. Finally, we had limited pregnancy and no neonatal outcome data and, therefore, were unable to conclude on the effect of various DMTs on safety parameters and outcomes relating to the offspring, but these are now actively being collected in the registry.[19]

In conclusion, our findings support the planned preconception use of OCR without necessary continuation into pregnancy or NAT continuation up to 28–32 weeks of gestation with early reinitiation after delivery as effective strategies to minimize disease activity during and after pregnancy. The DMT strategy should be discussed and planned ideally early on from MS diagnosis and before plans to conceive so that disease activity can be adequately controlled in advance of conception and an optimal strategy can be selected together with women with MS, thereby considering individual patient characteristics and preferences. Counseling and joint decision making between the clinician and patient remain paramount. Further data on other recently available DMTs, such as cladribine and ofatumumab, and neonatal/infant outcomes will be useful to inform individual choices of the DMT strategy for family planning.

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Continued

Appendix 1 *(continued)*

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Guy Laureys, MD, PhD	Universitary Hospital Ghent, Ghent, Belgium	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Barbara Willekens, MD	Department of Neurology, Antwerp University Hospital, Edegem; Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Julie Prevost, MD	CSSS Saint-Jérôme, Saint-Jerome, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Appendix 1 *(continued)*

Name	Location	Contribution
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Koen De Gans, MD	Groene Hart Ziekenhuis, Gouda, Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Dana Horakova, MD	Charles University in Prague and General University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Eva Kubala Havrdova, PhD	Charles University in Prague and General University Hospital, Prague, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Rana Karabudak, MD	Yeditepe University Kosuyolu Hospital, Neurological Sciences, Istanbul, Turkey	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Francesco Patti, MD	Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania; UOS Sclerosi Multipla, AOU Policlinico "G Rodloico-San Marco", University of Catania, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Pamela A. Mccombe, PhD	University of Queensland, Brisbane; Royal Brisbane and Women's Hospital, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Davide Maimone, MD	Centro Sclerosi Multipla, UOC Neurologia, Azienda Ospedaliera per l'Emergenza Cannizzaro, Catania, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Ayse Altintas, MD	Koc University, Istanbul, Turkey	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Radek Ampapa, MD	Nemocnice Jihlava, Jihlava, Czech Republic	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Daniele Spitaleri, MD	Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Oliver H.H. Gerlach, MD	Zuyderland Medical Center, Sittard-Geleen; School for Mental Health and Neuroscience, Maastricht University, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Maria Jose Sa, MD	Centro Hospitalar Universitario de Sao Joao; Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Richard A. Macdonell, MD	Austin Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Recai Turkoglu, MD	Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Elisabetta Cartechini, MD	Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Abdullah Al-Asmi, MD	Sultan Qaboos University, Al-Khodh, Oman	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

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Appendix 1 *(continued)*

Name	Location	Contribution
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Jiwon Oh, MD	St. Michael's Hospital, Toronto, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Erwan Muros-Le Rouzic, MPH	F. Hoffmann-La Roche Ltd, Basel, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Sabrina Guye, PhD	F. Hoffmann-La Roche Ltd, Basel, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Noemi Pasquarelli, PhD, MSc	F. Hoffmann-La Roche Ltd, Basel, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Helmut Butzkueven, MBBS, PhD	Department of Neuroscience, School of Translational Medicine, Monash University; Department of Neurology, Alfred Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Vilija G. Jokubaitis, PhD	Department of Neuroscience, School of Translational Medicine, Monash University; Department of Neurology, Alfred Health, Melbourne, Australia	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Michael Barnett, PhD	Brain and Mind Centre, Sydney, Australia	Site investigator	Data acquisition
Mark Slee, PhD	Flinders University, Adelaide, Australia	Site investigator	Data acquisition
Liesbeth Van Hijfte, MSc	Ghent University Hospital, Ghent, Belgium	Site investigator	Data acquisition
Bassem Yamout, MD	American University of Beirut Medical Center, Beirut, Lebanon	Site investigator	Data acquisition
Murat Terzi, MD	19 Mayis University, Samsun, Turkey	Site investigator	Data acquisition

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Appendix 2 *(continued)*

Name	Location	Role	Contribution
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Sarah Besora, MD	Hospital Universitari MútuaTerrassa, Barcelona, Spain	Site investigator	Data acquisition
Bruce Taylor, PhD	Royal Hobart Hospital, Hobart, Australia	Site investigator	Data acquisition
Tamara Castillo-Triviño, MD	Hospital Universitario Donostia and IIS Biodonostia, San Sebastián, Spain	Site investigator	Data acquisition
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Todd Hardy, MD	Concord Repatriation General Hospital, Sydney, Australia	Site investigator	Data acquisition
Danny Decoo, MD	AZ Alma Ziekenhuis, Sijsele - Damme, Belgium	Site investigator	Data acquisition
Yara Fragoso, PhD	Universidade Metropolitana de Santos, Santos, Brazil	Site investigator	Data acquisition
Gerardo Iuliano, MD	Ospedali Riuniti di Salerno, Salerno, Italy	Site investigator	Data acquisition
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Appendix 2 *(continued)*

Name	Location	Role	Contribution
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Chiyoko Nohara, MD	Tokyo Metropolitan Health and Medical Treatment Corporation Ebara Hospital, Tokyo, Japan	Site investigator	Data acquisition
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Deborah Field, MD	Lyell McEwin Hospital, Elizabeth Vale, Australia	Site investigator	Data acquisition
Eduardo Aguera-Morales, MD	University of Cordoba, Cordoba, Spain	Site investigator	Data acquisition
Dheeraj Khurana, MD	PGIMER, Chandigarh, India	Site investigator	Data acquisition
Riki Matsumoto, MD	Kobe University Graduate School of Medicine, Kobe, Japan	Site investigator	Data acquisition
Fumitaka Shimizu, MD	Yamaguchi University Graduate School of Medicine, Ube, Japan	Site investigator	Data acquisition
L G F Sinnige, MD	Medical Center Leeuwarden, Leeuwarden, Netherlands	Site investigator	Data acquisition
Simón Cárdenas-Robledo, MD	Hospital Universitario Nacional de Colombia, Bogota, Colombia	Site investigator	Data acquisition

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