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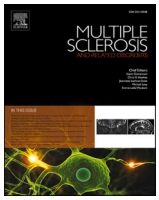

Treatment with natalizumab during pregnancy in multiple sclerosis: The experience of implementing a clinical practice protocol (NAP-30)

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ABSTRACT

Background: Pregnancy planning in women with highly active multiple sclerosis (HAMS) who need a high-efficacy disease-modifying therapy (heDMT) currently requires a careful risk-benefit evaluation. This includes minimizing fetal drug toxicity and preventing MS reactivation. We describe our experience with natalizumab in women with HAMS and unplanned pregnancy by implementing a clinical practice protocol (NAP-30) designed to maintain the effectiveness of natalizumab during pregnancy, reduce fetal exposure and prevent complications.
Methods: This was an observational retrospective study including women with HAMS on active treatment with natalizumab who became unexpectedly pregnant in the period 2018–2021 and continued this treatment during pregnancy according to the NAP-30 protocol. MS clinical and radiological variables were analyzed before and during pregnancy and in the postpartum period, along with maternal and fetal toxicity during pregnancy and safety findings in newborns. We also describe the NAP-30 protocol, which includes the use of a bridging dose to adjust and maintain natalizumab infusions every 6 weeks during pregnancy up to week 30 and scheduled delivery at week 40.
Results: Six women (one in her first gestation) with a median age of 31.5 years at the onset of pregnancy (min-max: 24–37 years) were included. All were negative for anti-John Cunningham virus (JCV) antibodies and were on treatment with intravenous natalizumab 300 mg every 4 weeks. At the time of conception, three patients had received 12, 17 and 53 infusions of natalizumab, respectively, while for the remaining three patients natalizumab was their first DMT (two patients had received 6 infusions and one patient had received 3 infusions of natalizumab). All six patients received 6 doses of natalizumab during pregnancy according to the NAP-30 protocol. After delivery, all six patients restarted natalizumab every 4 weeks (median: 3 days; range: 2–4 days). No patients had relapses during pregnancy or at 6 months postpartum, nor did they develop any general health or laboratory abnormalities. The MRI scan performed at 4–6 months postpartum showed no new T2 lesions or gadolinium-enhancing lesions. No miscarriages or threatened miscarriages were reported. One of the patients underwent elective preterm delivery at week 35 after mild-to-moderate anemia was detected by fetal Doppler scan. The newborn had low birth weight (2080 g) and mild anemia, which resolved within two months with oral iron supplementation. The other infants were born with normal birth weight and showed no blood count abnormalities. After a median follow-up of 10 months, all six babies showed normal development with no complications detected.
Conclusions: Based on our experience, the implementation of the NAP-30 protocol in women with HAMS and unplanned pregnancy undergoing treatment with natalizumab allows the continuation of natalizumab during pregnancy, with a very favorable clinical and radiological effectiveness and maternal-fetal safety profile during

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pregnancy and postpartum. Both in pregnancy with HAMS and in general, and particularly for successful implementation of the NAP-30 protocol, obstetric support and monitoring is essential for adequate pregnancy management.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system whose incidence is high in women of childbearing age. The frequent relapses and/or radiological activity that characterize highly active MS (HAMS) have a poorer prognosis and require the introduction of high-efficacy disease-modifying therapies (heDMTs) (Meca-Lallana et al., 2021). Although there are different definitions proposed for HAMS, most neurologists agree on the difficulty involved in planning and monitoring pregnancy in women presenting with these characteristics who require heDMT (Dobson et al., 2019; Langer-Gould, 2019). The increase in the number of DMTs in recent years (Tintore et al., 2019) should have improved treatment options in this setting. However, the lack of clinical trials and heDMT labels approving their use during pregnancy greatly hampers the decision-making process.

The discontinuation of a heDMT may result in MS reactivation, which is severe in some cases of rebound (Giovannoni et al., 2017). In women of childbearing potential with HAMS planning to get pregnant, the benefit-risk ratio of the heDMT to be used must be balanced. The potential fetal toxicity of maintaining the heDMT during pregnancy, as well as the risk of MS reactivation if discontinued before conception should be considered. In this case, reactivation may occur in the preconception period or during the first months of pregnancy, when the protective effect of pregnancy against HAMS is often insufficient (Confavreux et al., 1998).

Natalizumab is a humanized monoclonal antibody directed against lymphocytic integrin alpha-4, which acts by inhibiting the migration of activated lymphocytes across the blood-brain barrier into the central nervous system. Natalizumab is a heDMT approved for HAMS administered by intravenous infusion of 300 mg once every 4 weeks (EMA, 2021). Clinical trials and meta-analyses published since it was launched in 2006 have demonstrated its efficacy and safety (Polman et al., 2006; Pucci et al., 2011; Rudick et al., 2006).

In the first years of natalizumab use, the most common strategy for planning a pregnancy in women on this treatment was to delay gestation until disease stabilization and discontinue treatment for around 2 months before attempting conception. However, this approach has proven to be ineffective, as it increased the risk of relapses and disability progression (De Giglio et al., 2015; Sorensen et al., 2014). On the other hand, there are data indicating that natalizumab exposure at pregnancy onset could lead to a threefold reduction in the risk of disease rebound during gestation (Portaccio et al., 2018b).

Even in the absence of solid scientific evidence, data from clinical practice suggest that natalizumab exposure may be reasonably safe for fetuses and effective in the management of mothers (Portaccio et al., 2018a).

In this study, we analyze our experience with natalizumab during unexpected pregnancies by implementing a clinical practice protocol, which we called NAP-30 (Natalizumab-Arrixaca-Pregnancy-week 30), designed to minimize fetal exposure to natalizumab while maintaining its efficacy in pregnant patients. The NAP-30 protocol consists of using a bridging dose to adjust and maintain natalizumab infusions every 6 weeks during pregnancy until week 30 (thus minimizing placental transfer and the risk of hematologic abnormalities), scheduling delivery at week 40 and restarting natalizumab immediately after delivery to reduce the risk of rebound.

Our article aims to describe the characteristics of this clinical practice protocol for natalizumab treatment during pregnancy, share safety results of fetal exposure, and analyze its clinical effectiveness during pregnancy and its clinical and radiological effectiveness after delivery.

2. Materials and methods

2.1. Study design and patients

This is an observational, retrospective, clinical-practice-based study in six patients with HAMS on active treatment with natalizumab at our MS center who became unexpectedly pregnant in the period 2018–2021 and decided to continue with the treatment during pregnancy.

The study was approved by the Ethics Committee (EC) of the participating center and conducted following the Declaration of Helsinki and national regulations. All patients gave their written informed consent.

2.2. Assessments

Once pregnancy was confirmed, patients were informed of the potential risks of discontinuing natalizumab treatment during pregnancy as well as the risks and benefits of continuing with treatment based on the NAP-30 protocol developed according to our clinical practice and the existing evidence in medical literature.

Before pregnancy, data collection included demographics, general medical history (alcohol and tobacco use and substance abuse), obstetric history, clinical history of MS (time since diagnosis to conception, presence of relapses before initiating natalizumab, number of relapses in the last year, level of disability on the Expanded Disability Status Scale (EDSS) before initiating natalizumab and previous DMTs to natalizumab), radiological data of MS in the last available magnetic resonance imaging (MRI) (contrast-enhancing T1 lesions and new or unequivocally enlarging T2 hyperintense lesions), JCV (John Cunningham virus) serological status, and number of natalizumab infusions before pregnancy.

During pregnancy, all women were followed up at least twice according to clinical practice and the following information was recorded: number of relapses, EDSS score at the onset of and during pregnancy, number of natalizumab infusions received during pregnancy, maternal and fetal safety in general and related to natalizumab exposure, other medications received at conception and during pregnancy, and pregnancy-related complications.

Upon delivery and during the first 6 months postpartum we collected the date and type of delivery, complications during delivery, physical and laboratory abnormalities in mothers, Apgar score, physical and laboratory abnormalities in newborns, monitoring the health of newborns by interviewing their mothers and reviewing their medical history, date of first and subsequent infusions of natalizumab, number of relapses, EDSS score, and radiological activity (gadolinium-enhancing T1 lesions, new/enlarging T2 lesions) in an MRI scan performed within four to six months after delivery according to clinical practice.

2.3. NAP-30 clinical practice protocol

The first step of the NAP-30 protocol consists of estimating the gestational week and the expected date of delivery (week 40). Considering that some women have irregular menstrual periods and the potential concurrence of other misleading factors, we made this estimate based on the date of the last menstrual period and the support of a fetal ultrasound performed at the Obstetrics Department.

The second step consists of scheduling the dates of natalizumab infusions every 6 weeks during pregnancy by using week 30 of pregnancy

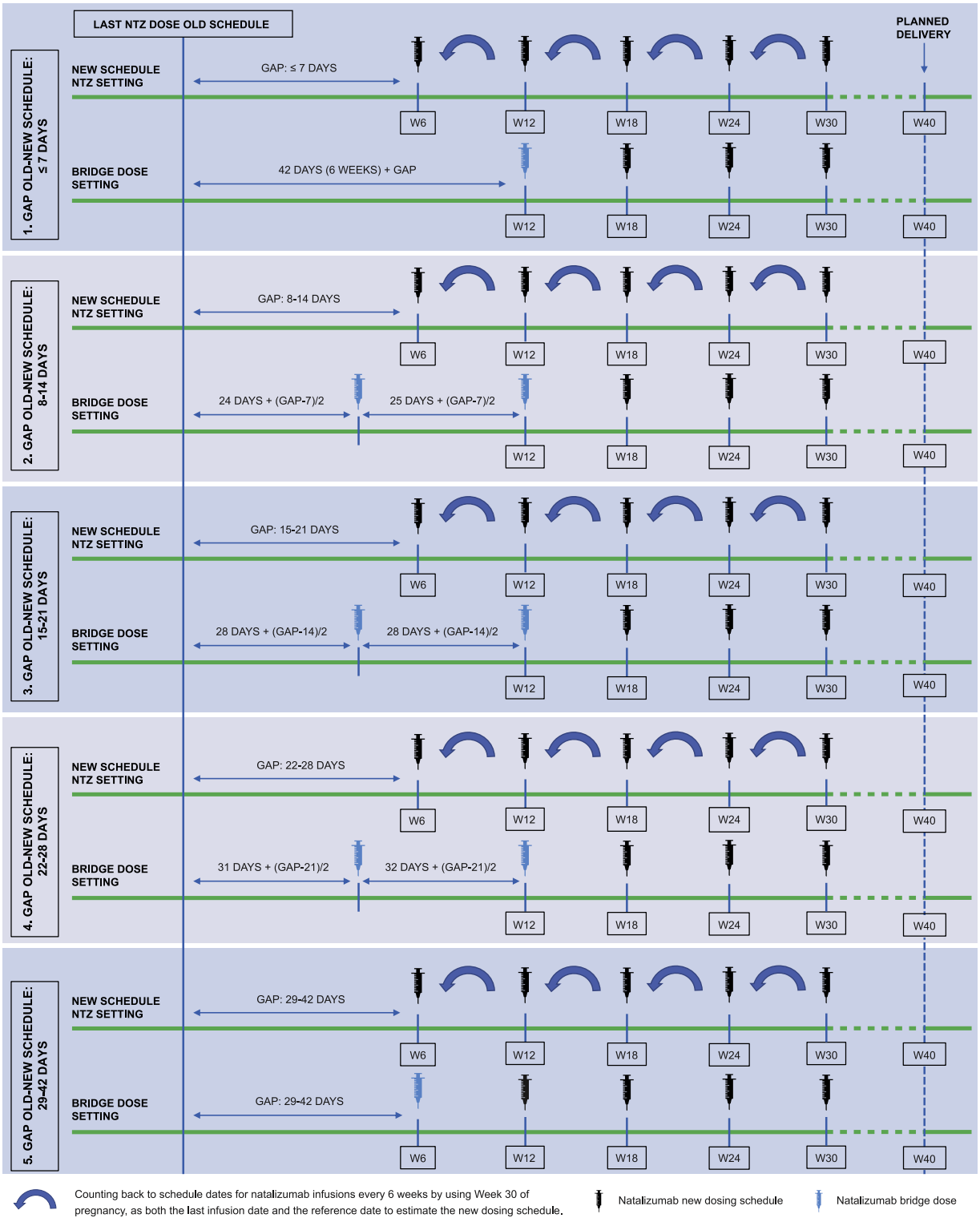

Fig. 1. NAP-30 protocol. Planning of the new infusion schedule during pregnancy and estimation of the bridging dose of natalizumab. Five different clinical scenarios with pregnancy confirmation before week 6 are shown, based on the gap between the last dose of natalizumab in the previous dosing schedule (every 4 weeks) and the first dose in the new NAP-30 protocol dosing schedule (every 6 weeks, pregnancy). Two green pregnancy timelines can be seen in each clinical scenario. The top green line represents the second protocol step (new NTZ schedule) and refers to the new schedule for the dates of natalizumab infusions every 6 weeks during pregnancy (NAP-30 protocol). The last natalizumab infusion before delivery is administered at week 30 of pregnancy and, using this as a reference, the new dosing schedule is estimated by counting back, that is: 30, 24, 18… The bottom green line represents the third step of the protocol (bridging dose adjustment) and it is developed from the one above. It indicates the adjustment between the last dose in the previous dosing schedule and the first dose in the NAP-30 protocol by administering 1–2 bridging doses. The protocol is equally applicable if confirmation of pregnancy occurs after week 6. NTZ: Natalizumab. W: Week. NAP-30 protocol: Natalizumab Arrixaca Pregnancy-Week 30 protocol. Gap: Time period between the last dose of natalizumab in the previous dosing schedule and the first dose in the NAP-30 protocol.

Table 1
Estimation of natalizumab bridging dose.

Gap (days) between last dose in previous schedule – first dose in new schedule (NAP-30)	Bridging dose 1 (time since last dose in previous schedule)	Bridging dose 2 (time since bridging dose 1)	Subsequent doses
≤ 7 days	42 days + gap	Not applicable	Every 6 weeks
8–14 days	24 days + (gap-7)/2	25 days + (gap-7)/2	
15–21 days	28 days + (gap-14)/2	28 days + (gap-14)/2	
22–28 days	31 days + (gap-21)/2	32 days + (gap-21)/2	
29–42 days	gap	Not applicable	

Estimation of natalizumab bridging dose(s) based on the time period (gap) existing between the last dose in the previous dosing schedule (every 4 weeks) and the first dose in the new NAP-30 protocol dosing schedule (every 6 weeks). Note: The upper limit of each gap (days) shows the equivalence in weeks (7 days: 1 week; 14 days: 2 weeks; 21 days: 3 weeks; 28 days: 4 weeks; 42 days: 6 weeks). If the numerator of the divisions is an odd number, the decimal "0.5" resulting from both divisions (one day) is added to one of the two bridging doses (so that the number of days in each is as similar as possible). NAP-30 protocol: Natalizumab Arrixaca Pregnancy-Week 30 protocol.

as the date of the last infusion and the reference date for estimating the new dosing schedule, which is done by counting back, (i.e., 30, 24, 18…) (Fig. 1).

The third and last step is to estimate the bridging doses to adjust the previous dosing schedule (every 28 days–4 weeks–) and the new dosing schedule in the NAP-30 protocol (every 42 days–6 weeks–). Typically, the bridging dose is administered during the first trimester of pregnancy, with the date of administration varying depending on the interval existing between the last dose of natalizumab in the previous dosing schedule and the first dose in the NAP-30 protocol. Details on the bridging dose adjustment are shown in Table 1 and Fig. 1.

The efficacy and safety findings of implementing this protocol were based on delivery occurring at week 40. Therefore, if delivery did not occur naturally at the beginning of this week or earlier, induction was scheduled during week 40 (before the end of the week). The administration of natalizumab infusions every 4 weeks was restarted immediately after delivery.

This protocol was applicable regardless of whether natalizumab infusions were administered every 4 or 6 weeks in the previous dosing schedule.

2.4. Statistical analysis

Description of each case is presented. Median (minimum and maximum) was used to describe continuous time variables.

3. Results

3.1. Patient characteristics

All six women on natalizumab treatment who became pregnant unexpectedly during the study period decided to continue with treatment following the NAP-30 protocol, and none of them opted to discontinue natalizumab. Therefore, six women were evaluated.

All six women become pregnant naturally with a monozygotic single pregnancy. The median age at MS diagnosis and at conception was 26 years (min-max 17–35 years) and 31.5 years (min-max 24–37 years), respectively (Table 2). Regarding pregnancy history, patients 2 and 3 had been pregnant previously. Patient number 2 became pregnant before MS diagnosis while patient 3 became pregnant with her first child a few months after being diagnosed with MS. In both cases, their pregnancy and delivery were uneventful.

All six patients were on treatment with intravenous natalizumab 300 mg every 4 weeks at conception. Patients 1, 5 and 6 had received other DMTs before starting natalizumab. Patient 1 was treated with intramuscular interferon beta-1a as the first DMT, and she had received 17 natalizumab infusions before becoming pregnant with no clinical and radiological activity in the previous year. Patients 5 and 6 had been previously treated with dimethyl fumarate and teriflunomide and, by the time of conception, they had received 12 and 53 natalizumab infusions, respectively. None of them showed relapses or new lesions on MRI in the previous year.

In the remaining three women, natalizumab was the first DMT as the disease debuted with HAMS. They became pregnant within one year of starting natalizumab treatment (3 to 6 months after initiation) and showed clinical and radiological activity in the year before pregnancy.

None of the 6 patients was receiving concomitant medication, which is considered a risk during pregnancy, nor did they smoke or use any drugs of abuse. In all 6 cases, anti-JCV antibody test was negative. Baseline characteristics of patients are summarized in Table 2.

3.2. Natalizumab treatment during pregnancy and clinical progress

All six patients received at least 6 infusions of natalizumab during pregnancy. Fig. 2 shows an example of the different dosing schedules applied to the first three patients (M1, M2 and M3). Patients 2 and 4 received 2 infusions of natalizumab before being aware of pregnancy and 4 infusions according to the NAP-30 protocol. Patients 1, 3, 5 and 6 received one natalizumab infusion before being aware of pregnancy and 5 infusions according to the NAP-30 protocol.

None of the women had relapses during pregnancy. No miscarriages or threatened miscarriages were reported (Table 3). Patient 1 underwent elective preterm delivery at week 35+3 days because a fetal Doppler performed at week 34 identified findings suggestive of mild-to-moderate anemia. Fetal lung maturation was accelerated with corticosteroids and vaginal delivery was induced and proceeded uneventfully. The newborn weighed 2080 g at birth and had mild anemia that resolved uneventfully over the next two months with oral iron supplementation. The rest of the

Table 2
Clinical characteristics of the mothers before pregnancy.

Patient	Age at MS diagnosis (years)	Time from MS diagnosis to pregnancy (months)	Age at conception	Number of NTZ infusions at conception	EDSS at the onset of pregnancy	Number of relapses in the year before pregnancy	MRI activity in the year before pregnancy	Anti-JCV antibodies
M1	26	60	31	17	0	0	No activity	Negative
M2	23	10	24	6	2.0	2	Yes (T2>9/ 4 Gd+)	Negative
M3	35	27	37	6	2.0	2	Yes (T2>9/ 7 Gd+)	Negative
M4	32	15	33	3	3.0	2	Yes (T2>9/ 10 Gd+)	Negative
M5	29	75	35	12	1.0	0	No activity	Negative
M6	17	131	29	53	1.5	0	No activity	Negative

EDSS, Expanded Disability Status Scale; M, mother; MS, multiple sclerosis; NTZ, natalizumab.

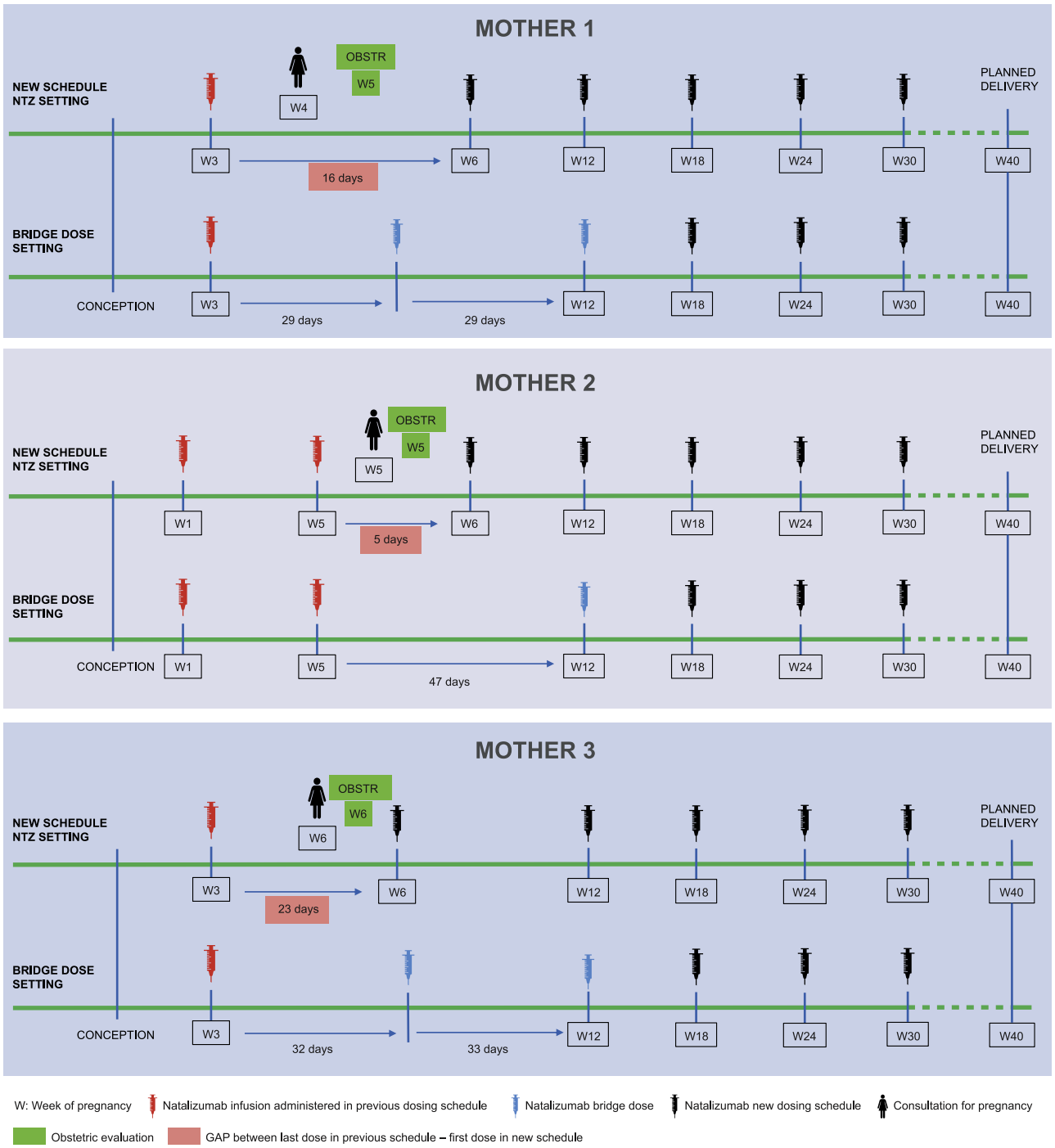

Fig. 2. Example of adjusted dosing treatment in mothers 1, 2 and 3 after implementing the NAP-30 protocol. In each case, the two green pregnancy timelines and the bridging dose adjustment described in Fig. 1 were applied.

women gave birth to healthy term newborns by vaginal delivery without complications. Patients 3 and 4 had labor induced at 40 weeks of gestation when they did not go into labor naturally. Newborns weighted >2500 g at birth and had no blood counts abnormalities. Characteristics of the newborns at birth are shown in Table 4.

3.3. Natalizumab treatment after delivery and clinical progress at 6 months postpartum

Patients restarted natalizumab treatment immediately after delivery (median: 3 days, min-max: 2–4 days), and none of them breastfed. At 6 months postpartum, patients showed no laboratory abnormalities or changes in health status. In no case was radiological activity detected on brain MRI performed within 4–6 months postpartum and no relapses were reported. Although not statistically tested, no change in EDSS from the start of treatment with natalizumab was evident (Tables 2 and 3) and no patient seroconverted to JCV-positive status during pregnancy or at 6 months postpartum.

No newborns had malformations at birth or during the follow-up period (median follow-up: 10 months, min-max: 6–32 months). Newborns from patients 1, 2 and 3 were followed up for more than 12 months and newborns from patients 4 to 6 between 6 and 8 months.

After delivery, the mothers were explained the benefits of breastfeeding and informed about the evidence-based data on the safety for the

Table 3
Clinical progress during pregnancy and in the first 6 months postpartum.

Patient	Number of NTZ infusions during pregnancy	Number of relapses during pregnancy	Number of relapses at 6 months postpartum	EDSS at 6 months postpartum	MRI activity at 4–6 months postpartum
M1	6	none	none	0	No activity
M2	6	none	none	2.0	No activity
M3	6	none	none	2.0	No activity
M4	6	none	none	3.0	No activity
M5	6	none	none	1.0	No activity
M6	6	none	none	1.0	No activity

EDSS, Expanded Disability Status Scale; M, mother; MRI, magnetic resonance imaging; NTZ, natalizumab.

newborn of maintaining natalizumab during breastfeeding. All the patients decided not to initiate breastfeeding.

4. Discussion

In our experience, the NAP-30 protocol is effective on clinical activity (relapses and EDSS) during pregnancy and on clinical and radiological activity at 6 months postpartum. While three of the six patients showed clinical and radiological activity in the year before pregnancy and were at increased risk of disease reactivation, they remained stable during the study period with no signs of clinical or radiological activity. Despite shorter periods of natalizumab exposure during pregnancy than in our patients, the study by Portaccio et al. (2014) demonstrated that discontinuation of natalizumab once pregnancy is confirmed and immediate resumption after delivery was an effective way to manage MS, as it reduced the risk of relapses during pregnancy and postpartum compared to patients who underwent a washout period before pregnancy.

Natalizumab has Category C pregnancy risk due to the lack of conclusive studies in humans (Houtchens and Kaplan, 2017). As an IgG4 monoclonal antibody, the risk of transplacental transfer during the first trimester is low and it gradually increases from the second trimester onwards (Schneider and Miller, 2010). Natalizumab has been shown to be present in serum of infants exposed to treatment during the third trimester (Haghikia et al., 2014), while no significant levels of natalizumab were detectable in infants whose last maternal exposure to treatment occurred more than 75 days before delivery (Proschmann et al., 2018).

Several series provide safety data on fetal exposure to natalizumab in real-world clinical practice during conception or at different stages of pregnancy. The rate of miscarriages in women with MS treated with natalizumab during pregnancy is similar to that found in the general population, while rates of congenital malformations are somewhat higher (Friend et al., 2016; Hellwig et al., 2011) but without a clear pattern that can be attributed to treatment exposure. In our study, none of the babies showed congenital malformations or birth defects or development disorders even though they were followed for different times (ranging from 6 to 32 months). The fact that four patients were under 35 years of age at the time of conception (min-max 24–37), and the lack of associated risk factors such as smoking or use of concomitant medications, may have contributed to the lack of fetal malformations in our sample. The study by Friend et al. (2016) showed that exposure to natalizumab during early pregnancy is associated with a slightly higher rate of malformations compared to the expected rate in the general population. However, it is difficult to establish causality without a pattern that can be attributed to natalizumab exposure. The no transplacental transfer of natalizumab during the first trimester, which increases slowly and gradually throughout the second trimester, could explain the lack of effect of natalizumab during organogenesis and the no evidence of a severe pattern of malformations.

Fetal exposure to natalizumab in primates and humans during the third trimester has been related to transient hematological abnormalities (Ciron et al., 2016; Wehner et al., 2009), most with no impact. In our series, signs of fetal anemia were detected in the fetus of patient 1 during the third trimester leading to early induction of labor. This did not result in immediate complications of any other nature for the mother and newborn. In our experience, close clinical monitoring of patients on treatment with heDMTs by the Obstetric Department allows for early detection and successful management of potential complications. The occurrence of hematological abnormalities in fetuses exposed to natalizumab during the third trimester has been previously documented (Haghikia et al., 2014; Triplett et al., 2020). These abnormalities are transient in most cases and do not have a significant impact. Our study shows that women who receive the last dose of natalizumab at the beginning of the third trimester (week 30) may develop this adverse effect. A potential explanation might be related to delayed clearance of antibodies by the fetus, which may increase the duration of natalizumab exposure, thus having a greater effect on fetal hematopoiesis (Mahadevan et al., 2013). It is striking that despite administering the last dose of natalizumab in the early 3rd trimester (week 30), when the placental transfer of natalizumab is lower than in the mid (e.g., week 34) or late 3rd trimester, fetal anemia has occurred. This again highlights the importance of obstetric monitoring and the need for active collaboration between the Neurology and Obstetrics departments.

Except for newborn 1, who was preterm and had low birth weight, the other two newborns were delivered at term and weighed over 2500 g. In the study by Ebrahimi et al. (2015), the mean birth weight of babies exposed to natalizumab during pregnancy was slightly lower than healthy control babies, but similar to babies from women with MS receiving interferon or glatiramer acetate.

The NAP-30 protocol was developed to maximize the effectiveness of natalizumab while minimizing its potential toxicity to the fetus.

In designing the NAP-30 protocol we have considered the recommendations of Dobson et al. on natalizumab treatment during pregnancy (Dobson et al., 2019) but several aspects differentiate our protocol. Dobson et al. recommended administering the last dose of natalizumab at approximately 34 weeks and suggested that the frequency of natalizumab infusions could be reduced to 8 weeks. The small series (5 to 13 cases) that have documented natalizumab exposure during the third trimester (Ciplea et al., 2020; Haghikia et al., 2014; Proschmann et al., 2018; Triplett et al., 2020) show variability in the infusion frequency

Table 4
Baseline clinical characteristics of the newborn babies.

	Gestational age	Weight at birth (grams)	Apgar test	Delivery	Hematological abnormalities	Malformations
NB1	Preterm 35W+6D	2080	9	Vaginal/ induced	Mild fetal anemia (Hb 13.1-Ht 42.3)	No
NB2	Term 37W+5D	3120	8	Vaginal	No	No
NB3	Term 40W+0D	3300	9	Vaginal/ induced	No	No
NB4	Term 39+5D	3125	10	Vaginal/ induced	No	No
NB5	Term 38W+5D	3260	9	Vaginal	No	No
NB6	Term 39W+2D	3000	9	Vaginal	No	No

D: days. Hb: hemoglobin. Ht: hematocrit; NB: newborn. W: weeks.

during pregnancy and the time from last natalizumab infusion to delivery, ranging from 2 to 91 days in the series by Ciplea et al. (2020) and from 5 to 42 days in the series by Triplett et al. (2020).

The NAP-30 protocol is characterised by a fixed and predefined 10-week time lag between the last dose of natalizumab and delivery. The second-to-last dose is given in week 24 (second trimester) and the last dose is given before delivery in week 30 (early in the third trimester). The fetus is then only exposed to one dose at the beginning of the last trimester, between weeks 24 and 40, and delivery is scheduled at week 40 (to avoid further delays and a possible "rebound" effect). Unlike the studies cited, the NAP30 protocol has no variability in the time between the last dose of natalizumab and delivery, allowing for a better interpretation of results.

Moreover, the NAP-30 protocol allows for natalizumab to be scheduled every 6 weeks from the time pregnancy is confirmed, by counting back from the scheduled delivery date and using one or two bridging doses (depending on the gap) to transition from natalizumab every 4 weeks (before pregnancy) to every 6 weeks (during pregnancy).

Several studies show that the 6-week dosing schedule of natalizumab in people with MS can be as effective as the 4-week dosing schedule and reduces the risk of progressive multifocal leukoencephalopathy (PML) (Chisari et al., 2020; Ryerson et al., 2019, 2022; Zhovtis Ryerson et al., 2020).

Extended interval dosing with natalizumab every 6 weeks during pregnancy offers two main advantages: it minimizes fetal drug exposure during the second trimester and may reduce the risk of rebound between week 30 and week 40, as it continues to allow small trafficking of lymphocytes into the CNS during pregnancy (Weinstock-Guttman et al., 2016). It could also reduce the risk of PML or its impact (Scarpazza et al., 2019) in case of JCV seroconversion or increased JCV index during pregnancy.

Concerning breastfeeding, small series have demonstrated that although low levels of natalizumab are detectable in breast milk of natalizumab-treated breastfeeding mothers, the intestinal transfer of natalizumab from breast milk to the neonate via the neonatal Fc receptor does not seem to be relevant (Ciplea et al., 2020). Nonetheless, further studies in larger series are needed to further understand pharmacokinetics. Ciplea et al. (2020) did not observe development alterations and health problems attributable to breast milk exposure after a median follow-up of 1 year. Given the short-and long-term infant and mother health benefits of breastfeeding and the very low theoretical risks of natalizumab to infants with breast milk exposure only, other authors (Langer-Gould, 2019) recommend continuing rather than discouraging breastfeeding when natalizumab is resumed in women with active disease

Our study was limited by its retrospective design and the sample size. The small sample size prevented us from carrying out an adequate statistical analysis in terms of efficacy and safety, which would allow us to establish recommendations. Further studies with a larger number of patients are required to confirm that the use of the NAP-30 protocol can be widely adopted in clinical practice. However, in view of the limited studies investigating the safety of continuing treatment with natalizumab during pregnancy, we consider that our experience with the NAP-30 protocol provides knowledge and relevant data for therapeutic decisions in women with similar characteristics to those described here. This clinical practice protocol could be applied to women with HAMS on natalizumab treatment and pregnancy desire, thus avoiding the risk of MS reactivation when natalizumab is discontinued before conception or early in pregnancy.

5. Conclusions

In conclusion, our results suggest that continuing treatment with natalizumab every 6 weeks in pregnant women with HAMS according to the NAP-30 protocol until week 30 of pregnancy could be useful and effective for management of the disease during pregnancy and postpartum. Pregnancies in patients on treatment with heDMTs should be considered as risk pregnancies that require appropriate multidisciplinary management involving obstetric specialists. Further studies are needed to increase our understanding of the use of heDMTs during pregnancy in patients with HAMS.

Credit author statement

G. Valero-López and J.E. Meca-Lallana contributed to the study conceptualization, data curation and formal analysis. G. Valero-López, J. E. Meca-Lallana, J. Millán-Pascual and J.L. Delgado-Marín contributed to the study conceptualization, formal analysis, resources and supervision. All authors contributed to writing – original draft and writing – review and editing of manuscript, provided their approval for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

G. Valero-López and J. Millán-Pascual have participated in clinical trials and other research projects sponsored by Biogen, Bristol-Myers-Squibb, Merck, Novartis, Roche and Sanofi. J.E. Meca-Lallana declares that he has received honoraria as consultant, chairman or lecturer in meetings and has participated in clinical trials and other research projects sponsored by Biogen, Bristol-Myers-Squibb, Merck, Novartis, Roche and Sanofi. The rest of the authors declare no conflict of interests to disclose.

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