Subcutaneous versus intravenous natalizumab extended- interval dosing in pregnant women with MS: a French and Italian case series

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BACKGROUND

Intravenous (IV) Natalizumab (NTZ) is the only approved high-efficacy disease modifying treatment (DMT) that can be continued after conception in pregnant women with MS (WwMS). Its use during pregnancy usually follows a scheme of extended-interval dosing (EID), with infusions given at intervals of 6 weeks rather than every 4 weeks.[1] NTZ administration is usually temporarily suspended at a period varying from the end of the second trimester up to 30-34 weeks of gestation, to be resumed 1-2 weeks after delivery.[1-2] Recently, a subcutaneous (SC) form of the drug has become available. A bioequivalence study evaluating the two different administration routes of NTZ showed that pharmacodynamic measures are comparable independently of the injection route.[3] However, some findings show that switching from the IV to the SC route can lead to decreased serum drug concentrations,[4-5] which could be even further lowered in the context of pregnancy.[6] To date, no information is available on the effect of SC NTZ EID given during pregnancy on clinical and/or radiological reactivation during pregnancy or in postpartum, nor on the length of a safe washout period in the last trimester.

AIMS

- To assess the efficacy of SC NTZ EID versus IV NTZ EID on relapse activity during pregnancy and during postpartum, as well as on MRI activity in postpartum
- To define the length of a safe washout period with SC NTZ in the last gestational trimester

METHODS

This is a retrospective multicentric study performed across 9 tertiary MS centers in France and Italy. Two groups of WwMS who received either IV or SC natalizumab EID and completed their pregnancy between February 2019 and March 2025 were collected. A clinical follow-up period of four months after delivery was assessed in this study. Fisher's exact test, followed by multivariable logistic regression to adjust for confounders (duration of washout, number of doses during pregnancy and interval between delivery and postpartum MRI), were used to compare outcomes by administration route. SC-IV Group differences in the odds of disease activity were expressed as odds ratios (OR).

RESULTS

1. Cohort description

56 pregnancies were identified: 35 received IV NTZ, while 21 received the SC formulation. The median number of NTZ doses during pregnancy was 5 in both cases (p=0.80), and the median interval between administrations was similar between groups (SC: 5.3 weeks, IV: 5.4 weeks, p=0.35). Mean peripartum NTZ washout length did not differ between groups (SC: 106 ± 27 days, IV: 103 ± 34 days, p=0.73). Similarly, the mean delay for NTZ resumption after delivery was not different (SC: 11 ± 9 days, IV: 13 ± 9 days, p=0.72) (Table 1).

2. No difference in relapse activity between SC and IV NTZ group

A clinical relapse at 38th gestational week was reported for one WwMS receiving SC NTZ (washout length: 105 days) and few days and one month after delivery for two receiving IV NTZ (washout length: 134 and 170 days). This difference was not statistically significant (p=0.88). In all three cases the postpartum MRI demonstrated radiological changes compared to the last available MRI done before pregnancy onset.

3. **WwMS receiving SC NTZ EID have higher postpartum radiological activity over shorter washout periods**

Mean interval between delivery and postpartum MRI was similar between groups (SC: 52 ± 43 days, IV: 83 ± 86 days, p=0.13). Brain MRI was available for all participants, while spinal cord MRI was available only for 6 WwMS of the SC group and 8 WwMS of the IV group (Table 1). In the SC group, postpartum radiological activity was observed in 10 out of 21 WwMS (47.6%), while 5 out 35 cases had MRI activity in the IV group (14,3%) (p=0.012; OR=5.32[CI:1.41-20.06]) (Figure 1. Radiological reactivation for the 10 cases of the group receiving SC NTZ was distributed as follows: 8/21 cases had new T2 brain lesions (median: 1 lesion, min-max: 1-11), with concomitant gadolinium-enhancement in 3 of them; 2/6 cases had one new T2, non-gadolinium-enhancing spinal cord lesion and no new brain lesions. Radiological reactivation for the 5 cases of the group receiving IV NTZ was distributed as follows: 5/5 cases had new T2 brain lesions (median: 3 lesions, min-max: 1-5), with concomitant gadolinium enhancement in 2 cases.

4. Wash-out lenght

Among the 10 SC NTZ-treated WwMS with post partum radiological reactivation, 50 % (5/10) experienced MRI activity after a washout <12 weeks (median washout for these 10 WwMS : 94 days, range: 73-139). Conversely, in the IV NTZ group, no patients with radiological reactivations were observed with washout <12 weeks (median washout for MRI active WwMS in the IV group : 123 days, range: 85-170). Looking at the mean delay for NTZ resumption after delivery, this was not different between the MRI-active WwMS of the SC vs IV group (SC: 15 ± 7 days, IV: 17 ± 10 days, p=0.71)

	Subcutaneous natalizumab	Intravenous natalizumab	*P*
WwMS, n	21	35	
Age at pregnancy onset, years (mean ± SD)	31.7 ± 4.7	32.8 ± 4.6	0.42
N of NTZ administrations during pregnancy (median)	5	5	0.80
Interval between NTZ administrations, weeks (median)	5.3	5.4	0.35
NTZ washout length, days (mean ± SD)	106 ± 27	103 ± 34	0.73
Interval between delivery and postpartum MRI, days (mean ± SD)	52 ± 43	83 ± 86	0.13
Delay between delivery and NTZ resumption, days (mean ± SD)	11 ± 9	13 ± 9	0.72
N of WwMS with a postpartum brain/spinal cord MRI exam available	21/6	35/8	
N of C-sections on the whole group	10/21	10/35	0.16

Table 1 Demographic and clinical data of pregnant women with MS

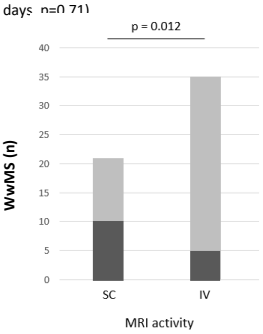

Fig 1 MRI activity in the SC versus IV NTZ EID cohort

DISCUSSION AND CONCLUSIONS

Women receiving SC NTZ had a equal rate of clinical relapse but a higher number of new lesions on postpartum MRI compared to those treated with IV NTZ, despite similar numbers of doses during pregnancy and comparable NTZ washout periods. Notably, half of radiological reactivations in the SC group occurred at < 12 weeks of washout. This reduced effect could depend on changes in total plasma volume during pregnancy (eventually resulting in lower total NTZ serum concentrations), altered protein binding and / or decreased integrin receptor saturation. In conclusion, our results indicate that a less effective control of radiological reactivation of MS occurs in pregnant WwMS receiving SC NTZ given with EID. This should encourage an adaptation of the administration schedule during pregnancy and after delivery (e.g. shorter NTZ washout in the third trimester, faster resumption in the postpartum) for better disease control in this population.

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