Management of multiple sclerosis after pregnancy: The GAMPP Study

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Introduction

Multiple sclerosis (MS) which affects more women than men presents a problem of disease management especially after pregnancy. While pregnancy is not regarded to have an overall effect on the long-term disease course, besides others Confavreux (1) reported a 1.7-fold risk of exacerbation compared to pre-pregnancy for untreated patients during the first 3 months after delivery. To prevent relapses different therapeutic approaches have been proposed in the past. Licensed drugs for relapsing remitting MS (RR-MS), however, are contraindicated or should be avoided during breastfeeding. Otherwise breastfeeding is recommended as having a benefit on the infants' health especially in early life. In general, neurologists recommend not to restart disease modifying therapy until stop of breastfeeding. Thus most breastfeeding patients are without therapy during this period of elevated relapse risk. Several clinical trials have provided evidence for intravenous immunoglobulin (IVIG) to have a beneficial effect on relapse activity during the course of RR-MS (2-7). Similar efficacy during the puerperium had been reported in pilot trials and case reports (8-10).

Objectives

Under the auspices of the European Charcot Foundation the GAMmaglobulin Post Partum study (GAMPP study) was initiated in order to investigate the efficacy of two IVIG dosing regimens on the postpartum relapse activity of MS patients in terms of relapse free patients during 3 months postpartum. Secondarily, further parameters, e.g. annualized relapse rate (ARR), further periods and patient subgroups had been analyzed.

Methods

The GAMPP study is a multinational prospective, randomised, stratified double-blind confirmatory clinical trial with a parallel group design. Pregnant patients aged ≥ 18 years were eligible if they had confirmed RR-MS with an EDSS of 0 to 6.5 and at least one relapse during the two years before the actual pregnancy. A previous delivery should have been finished at least 36 months before the expected delivery date. Immunomodulatory therapies should have been stopped 4 weeks after last menstrual period.

IVIG (Octagam 5%, Octapharma Pharmazeutika Prod.Ges.m.b.H., Vienna, Austria) treatment was started within 24 h of delivery. Patients were stratified into a group with or without immunomodulatory pretreatment and randomised by a central pharmacy into one of two dose regimen groups for the initial phase of the treatment with IVIG during the first three consecutive days after delivery. This treatment phase was blinded. **Group I** received IVIG at a dose of 150 mg/kg body weight (BW) on Day 1 followed by 2 infusions of placebo (0.9% sodium chloride) on Day 2 and Day 3; **Group II** was treated with a booster dose of IVIG (totalling 900 mg/kg BW) given over 3 days as 450 mg/kg, 300 mg/kg and 150 mg/kg on Days 1, 2 and 3, respectively. This was followed by an open-phase during which both groups received 5 further doses of 150 mg/kg at 4-weekly intervals at the neurological study sites with a monthly neurological examination and evaluation of tolerability.

Results

Out of 173 enrolled patients 163 patients (Group I: 82; Group II: 81) could be evaluated for efficacy during 3 months postpartum. Group II was slightly but not significantly better than Group I in terms of relapse free patients during the 1st trimester postpartum (Group I: 75.6 %, Group II: 81.5 %). The study treatment resulted in a limitation of the 3 months postpartum ARR to a mean rate of 0.9 ± 1.8 which was slightly below the pre-pregnancy ARR of 1.0 ± 0.7 (Figure 1).

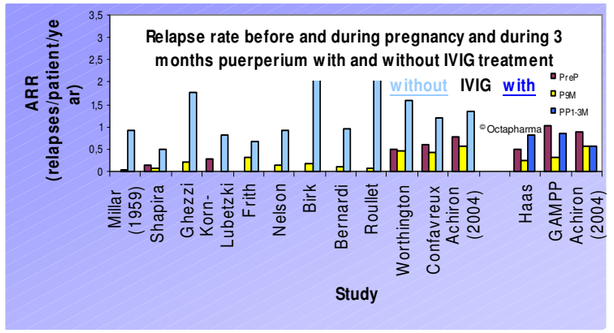

Figure 1: Relapse activities before (preP) and during (P9M) pregnancy and during 3 months puerperium (PP1-3M) in retrospective and prospective investigations (for referred studies see References)

There was no difference of ARR for patients who had only 1 relapse during 2 years before pregnancy (Table 1). However, patients who reported 2 (preP ARR=1) or more relapses (preP ARR>1) during the 2 pre-pregnancy years and receiving the booster dose had a slightly lower risk of exacerbation during the first 3 months of puerperium than Group I patients (Table 1).

Patients who did not breastfeed due to different reasons had a higher risk of exacerbation compared to patients breastfeeding for at least 3 months. The relapse risk for non-breastfeeding patients was slightly lower when treated in Group II (Table 1). Combining both treatment groups (Group I and Group II) there was a mean 19.3 % difference of relapse free patients between the non-breastfeeding group and the group breastfeeding for more than 3 months.

	Patients (n) All (Group I/Group II)	Group I	Group II
Number of patients	163	82	81
Relapse free patients during 3M postpartum	128 (62/66)	75.6 %	81.5 %
Relapse activity		**ARR**	
Before pregnancy		1.0 ± 0.7 (Median: 1.0)	1.0 ± 0.6 (Median: 1.0)
3 months postpartum (3M PP)		1.1 ± 2.0 (Median: 0.0)	0.7 ± 1.7 (Median: 0.0)
Breastfeeding	©Octapharma	**Relapse free patients during 3M PP**	
No breastfeeding	24 (12/12)	66.7 %	75.0 %
Breastfeeding >3 months	91 (38/53)	89.5 %	90.6 %
Relapse activity before pregnancy		**Relapse free patients during 3M PP**	
1 relapse 2 yrs prior to pregnancy	73 (38/36)	84.2 %	83.3 %
2 relapses 2 yrs prior to pregnancy	52 (27/25)	70.4 %	84.0 %
>2 relapses 2 yrs prior to pregnancy	37 (17/20)	64.7 %	75.0 %

Table 1: Relapse activities for the GAMPP patients and for subgroups in relation to breastfeeding and pre-pregnancy relapse activity

The study drug was well tolerated. The ratio of infusions with adverse drug reactions did not differ between both treatment groups (5 % vs. 6 %) and was similar to that found previously for patients treated for immunodeficiencies (22). Headache was the most frequent symptom reported by 6 % of the patients.

Summary and conclusion

- The GAMPP study is the first randomised confirmatory clinical trial considering the efficacy of IVIG on the postpartum relapse risk of patients with RR-MS.
- The study compares two IVIG dosage regimen.
- The ratio of relapse free patients during 3 months postpartum is similar in both dosage groups.
- For the first time the postpartum relapse rate does not exceed the pre-pregnancy relapse activity.
- A higher ratio of breastfeeding patients remained relapse free compared to non-breastfeeding patients.
- Patients with a higher pre-pregnancy relapse activity might have a benefit of the booster dose.

References

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