

Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database

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Background: *Appropriate counseling and treatment for women with multiple sclerosis (MS) who may become pregnant requires an understanding of the effects of exposure to disease-modifying therapies (DMTs) during pregnancy. Current reports and studies are limited in their usefulness, mostly by small sample size. Branded glatiramer acetate (GA) is a DMT approved for the treatment of relapsing forms of MS. For more than 2 decades, it has been shown to be efficacious and to have a favorable safety profile. The Teva Pharmaceutical Industries Ltd global pharmacovigilance database comprises data from more than 7000 pregnancies, during which women with MS were exposed to treatment with branded GA.*

Methods: *We analyzed data from Teva's global pharmacovigilance database. Pregnancy outcomes for patients treated with branded GA were compared with reference rates of abnormal pregnancy outcomes reported in two large registries representing the general population.*

Results: *Pregnancies exposed to branded GA were not at higher risk for congenital anomalies than what is expected in the general population.*

Conclusions: *These data provide evidence that branded GA exposure during pregnancy seems safe, without teratogenic effect. Int J MS Care. 2018;20:9-14.*

There is general agreement that pregnancy does not influence disability or progression in women with multiple sclerosis (MS)¹⁻⁴ and some evidence that it confers a favorable long-term prognosis.⁵ Despite the fact that pregnancy is no longer discouraged, none of the current disease-modifying therapies (DMTs) is approved for use during pregnancy. Thus, treatment is typically discontinued on confirmation of an unintended pregnancy or when a woman is

trying to conceive.^{6,7} Achieving pregnancy can take some time,⁶ however, and, if left untreated, women with MS are at risk for permanent central nervous system damage.⁸ Furthermore, for pregnant women with substantial or highly active MS, the benefit of continued treatment may outweigh the unknown risk to the fetus from a DMT.⁶

Branded glatiramer acetate (GA) (Copaxone; Teva Pharmaceutical Industries Ltd, Petach-Tikva, Israel) is a synthetic complex polypeptide mixture that acts as an antigen-based immunomodulator.⁹ It is approved to treat patients with relapsing forms of MS and is the only DMT assigned to the US Food and Drug Administration's (FDA's) pregnancy category B.¹⁰ Prescribing guidelines in the United States¹⁰ and several other countries^{11,12} allow the use of GA during pregnancy if clearly needed. The clinical benefits of branded GA include a 30% reduction in annualized relapse rate,¹³ decreased brain lesion activity,¹⁴ and long-term effects on disability progression.¹⁵ To our knowledge, during exposure for more than 2 million patient-years and among patients

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treated for more than 20 consecutive years, there has been no evidence of immunosuppression, the emergence of malignancies, infections, autoimmune diseases, or neutralizing antibodies, features that are important with long-term use.¹⁶⁻¹⁸ In addition, there seem to have been no reports of GA-related progressive multifocal leukoencephalopathy.

Appropriate counseling and treatment for women with MS who may become pregnant requires an understanding of the effects of exposure to DMTs during pregnancy; nevertheless, current reports and studies are limited in their usefulness, mostly by small sample size. Teva's global pharmacovigilance database (Medical Dictionary of Regulatory Activities [MedDRA], version 17.0) comprises data from more than 7000 pregnancies collected over 20 years from branded GA clinical trials, spontaneous reports, cases in the literature, and data from patient support programs. We report herein the results of an analysis of pregnancy outcomes from this database and compare them with outcomes from two reference databases representing the general population. The general population was chosen as a comparator based on the results of multiple studies indicating that MS does not negatively affect pregnancy.⁶

Methods

Teva's global pharmacovigilance database was searched for reports of pregnancy among women treated with branded GA (20 mg/mL) that were received up to and including September 30, 2014. The external reference sources used for comparison of congenital anomalies were the European Surveillance of Congenital Anomalies (EUROCAT)¹⁹ and the Metropolitan Atlanta Congenital Defects Program (MACDP).²⁰ The EUROCAT, a network of population-based registries for the epidemiologic surveillance of congenital anomalies, surveys more than 1.7 million births each year and covers 29% of the European birth population. The MACDP is a US population-based system that has tracked birth defects among infants and children born to mothers living in metropolitan Atlanta, Georgia, USA, since 1967 using active case-finding methods and multiple sources of information. More than 50,000 births are tracked annually. These sources were chosen for the comparison because approximately 70% of the pregnancy cases in the branded GA database were reported from the United States and Canada, and the remaining 30% were reported mostly from the European Union.

The study protocol and informed consent for the clinical trials from which some of the data in this study were taken were approved by a properly constituted institutional review board. The studies were performed in accordance with applicable Code of Federal Regulations, Good Clinical Practice standards, and International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, as well as FDA regulations, ICH Good Clinical Practice guidelines, and the World Medical Association Declaration of Helsinki.

Results

Number of Pregnancies

The Teva pharmacovigilance database search retrieved 7468 pregnancy cases categorized as spontaneous (case reports and series reported in the literature and unsolicited reports from patients), solicited (cases reported as a direct result of contact with the patient either as part of a patient support program or during market research), or clinical trial reports (cases reported during the branded GA clinical trials). Approximately 88% of the pregnancy cases in the database are solicited (Figure 1). In the database, mother and child reports are recorded as separate cases; however, they are linked because they describe the same pregnancy. The 7468 cases were reviewed to ensure that a pregnancy was not counted twice. As a result, 126 cases were eliminated, leaving

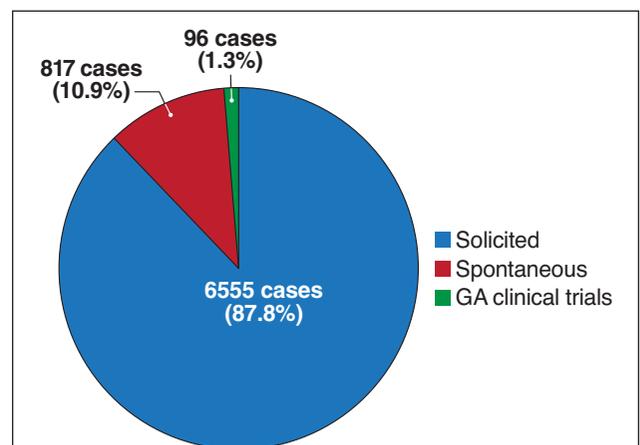


Figure 1. Pregnancies by reporting source (n = 7468)

Solicited includes cases reported as direct result of contact with the patient initiated by Teva (eg, as part of a patient support program or during market research). Spontaneous includes cases reported in literature (eg, case reports/series) and unsolicited reports from patients. GA, glatiramer acetate.

7342 pregnancies for analysis. Due to a twin pregnancy, the number of pregnancy outcomes was 7343. Of these, 2301 (31.3%) had an unknown outcome (eg, no report) or the pregnancy was still ongoing at the time of this report. We report herein only the analysis for the 5042 pregnancies with known outcomes.

Prospective Versus Retrospective Reports

Good pharmacovigilance practice guidance requires the inclusion of both prospective and retrospective reports. This study conforms with good pharmacovigilance practice and uses the definitions of prospective and retrospective specified by the European Medicines Agency.²¹ Prospective cases are defined as those for which the data were obtained before knowledge of the pregnancy outcome or before detection of a congenital malformation at prenatal examination (fetal ultrasound, serum markers, etc.). Retrospective cases include those for which the data were obtained after the outcome of the pregnancy was known or after a congenital malformation was detected on prenatal testing. Retrospective cases are prone to recall bias; therefore, the results are reported for prospective and retrospective cases separately.

Pregnancy Outcomes

Of the 5042 pregnancies with known outcomes, 2235 were prospective cases and 2807 were retrospective. Of the prospectively reported pregnancies, 84.9% resulted in live births; 10.4%, in spontaneous abortion; and 3.2%, in elective termination. The remainder (<1.5%) were reported as stillbirth, intrauterine death/fetal demise, ectopic pregnancy, or hydatidiform mole. As expected, due to reporting bias, the total rate of abortions/pregnancy terminations and abnormal outcomes was higher for retrospective cases (Table 1).

Congenital Anomalies

Congenital anomalies (events under Summary of Changes, “Congenital, Genetic, and Familial Disorders”; MedDRA version 17.0) were reported in 138 pregnancies. Most of these pregnancies (n = 104 [75%]) were associated with a live birth; 25 resulted in pregnancy termination or fetal losses. There were nine pregnancies in which an anomaly was reported, but no further information was supplied as to whether it was associated with a live birth or pregnancy termination (Figure 2).

A total of 174 congenital anomalies were reported among 138 pregnancies (Table 2). The most common were trisomy 21 (n = 13), heart disease (n = 9), talipes (n = 8), and developmental hip dysplasia (n = 7). Sixty of

Table 1. Known pregnancy outcomes: prospective versus retrospective reports

Outcome	Reports, No. (%)	
	Prospective (n = 2235)	Retrospective (n = 2807)
Live birth		
Normal (reported as healthy newborn)	1227 (54.9)	1139 (40.6)
Born alive, no congenital anomaly reported	628 (28.1)	929 (33.1)
Congenital disorder	42 (1.9)	62 (2.2)
Abnormal (perinatal disorder)	2 (<1.0)	5 (<1.0)
Abortion/pregnancy termination ^a		
Spontaneous	232 (10.4)	521 (18.6)
Elective ^b	71 (3.2)	67 (2.4)
Type not specified	0	9 (<1.0)
Fetal death ^a		
Stillbirth	10 (<1.0)	21 (<1.0)
Intrauterine death/fetal demise	6 (<1.0)	12 (<1.0)
Other		
Ectopic pregnancy	14 (<1.0)	39 (1.4)
Hydatidiform mole	3 (<1.0)	3 (<1.0)

^aPregnancy outcomes that included congenital anomalies (see Figure 2).

^bApart from 16 cases of elective pregnancy termination due to a congenital anomaly, reasons for elective termination were not reported.

the anomalies occurred in prospectively reported cases. Among these, the distribution by outcome and body system was similar to that seen in the combined cases.

Comparison of Branded GA Rate of Congenital Anomalies with External Reference Rates

The rate of pregnancies resulting in congenital anomalies was compared with reference rates obtained from the EUROCAT and MACDP databases. Because

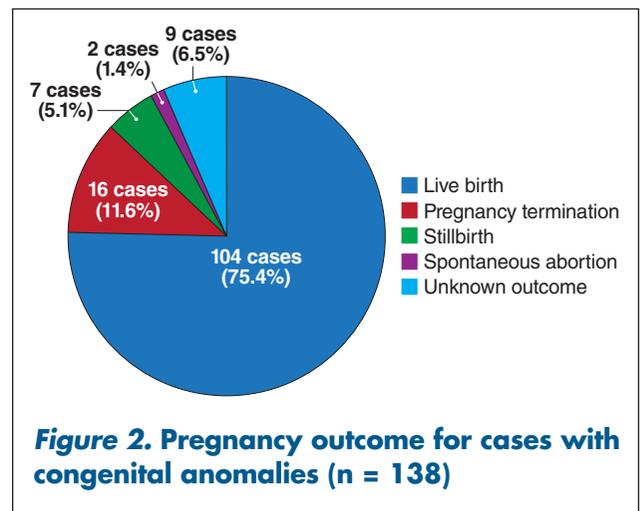


Figure 2. Pregnancy outcome for cases with congenital anomalies (n = 138)

Table 2. Congenital anomalies by system

System	Observed events, No. ^a
Limb anomalies	27
Cardiac disorders	26
Chromosomal abnormalities	26
Neurologic disorders	24
Other anomalies/disorders	17
Respiratory disorders	16
Renal/urogenital disorders	15
Gastrointestinal tract disorders	13
Minor skin/soft tissue anomalies	8
Eye disorders	2

^aThere were 174 events reported among 138 pregnancies.

the number of cases for each individual anomaly was low (most anomalies were reported as a single occurrence) and no patterns were identified for a specific anomaly, organ, or type of anomaly, the rate of the total number of cases resulting in congenital anomalies in the Teva pharmacovigilance database was compared with the reference rate for all anomalies. The results are reported separately because the EUROCAT is based on pregnancies and the MACDP includes only live births.

The comparison is expressed in terms of a standardized incidence ratio (SIR), an estimate of the occurrence of an event in a population relative to what could be expected if the population had the same experience of that event as some larger comparison population designated as average. The SIRs are calculated as ratios of the observed number of cases to the expected number of cases. An SIR of 1.00 indicates that the number of cases observed in the population evaluated equals the number of cases expected in the comparison or apparently healthy population; when SIRs are greater than 1.00 or less than 1.00, more or fewer events than expected occur, respectively.

For the EUROCAT comparison it is most appropriate to compare the data for prospective pregnancies with known outcome, because those cases are most compatible with the definition of EUROCAT rate of anomalies. In this case, the resulting SIR (0.97; 95% CI, 0.73–1.27) indicated that the rate of congenital anomalies in women exposed to branded GA while pregnant is very similar to that of the general European population (Table 3). The percentage of congenital disorders in all the examined cohorts is also lower than the percentage reported for the general US population in the reference prevalence rate from the MACDP (Table 4). Data from Teva's pharmacovigilance database include both major and minor anomalies, whereas the reference prevalence rate from MACDP is more conservative in that it represents only the rate of major congenital anomalies.

Discussion

It is realistic to assume that there will be some early fetal exposure to DMTs considering the high rate of unintended pregnancy (eg, 40% worldwide in 2012²³) and women with MS no longer being discouraged from becoming pregnant. Indeed, it is increasingly being suggested that for patients using branded GA or interferon beta, a washout period is not necessary before pursuing pregnancy.^{24,25} It must also be considered that, in cases where it is warranted, DMTs are continued throughout pregnancy.

Several small studies have shown no deleterious effects from branded GA in women with MS who were exposed early in their pregnancy^{26–28} or even throughout their pregnancy.^{29,30} Pregnant women with MS who were exposed to branded GA had no significant increased risk of spontaneous abortion or frequency of premature birth, and no significant differences in

Table 3. Comparison with EUROCAT reference rate of congenital anomalies

EUROCAT rate of CA ^a	Cohort	Branded GA safety database			SIR (95% CI)
		Pregnancy outcomes, No.	Cases with CA, No.		
			Observed ^a	Expected	
244.79/10,000 pregnancies ^b	All pregnancies	7343 ^c	138	179.7	
	Prospective cases				
	All cases	4447	60	108.9	
	Known outcome	2235	53	54.7	0.97 (0.73–1.27)

Abbreviations: CA, congenital anomaly; EUROCAT, European Surveillance of Congenital Anomalies; GA, glatiramer acetate; SIR, standardized incidence rate.

^aEUROCAT includes only CAs³¹; GA-observed cases include congenital disorders and CAs.

^bBirth definition includes live birth, fetal death/stillbirth from 20 weeks' gestation, and termination of pregnancy for fetal anomaly after prenatal diagnosis.

^cIncludes one pregnancy that resulted in a twin birth.

Table 4. Comparison with MACDP reference rate of major birth defects

MACDP rate of CA ^a	Branded GA safety database		
	Cohort	Live births, No. ^b	CAs, No. (%)
3% of US	All pregnancies	4034	104 (2.6)
	Prospective cases	1899	46 (2.4)

Abbreviations: CA, congenital anomaly; GA, glatiramer acetate; MACDP, Metropolitan Atlanta Congenital Defects Program; US, United States.

^aIn MACDP, prevalence is defined as number of infants and fetuses with a major birth defect who were delivered during a specified period divided by number of live births during that period.²²

^bIncluding normal newborns, live births, with congenital disorders, and live births for which no additional health information was provided.

infant mean birth weight and length, compared with women with MS not exposed to branded GA.²⁸ In addition, branded GA has not been shown to be associated with an increased risk of neonatal complications, malformations, or birth defects when taken throughout pregnancy.³¹⁻³³

The results from this large database of women with MS who were exposed to branded GA during their pregnancy confirm the outcomes of smaller case reports. The comparisons of total anomalies using a ratio of observed-to-expected cases (SIR) showed that the risk of congenital anomalies was similar to that expected in the general population. Important elements in this analysis include the use of prospective data and the comparison with two large general population registries. The large size of the database (>7000 pregnancies) allows for robust comparisons with the general population.

This study has some limitations. At the time that this report was completed, analysis of the duration and timing of exposure to branded GA was still ongoing. These results will be reported in a future article. Other limita-

tions include the absence of specific information on the types and rates of the abnormalities associated with abortions, as well as data on mother's age, previous abnormal pregnancy outcomes, and exposure to other medications during pregnancy. Additional data on the prepregnancy course of disease for these patients, as well as the number of treated exacerbations and severity of disease, might also provide perspective on the pregnancy outcomes.

We believe that, when the data in this report are considered, it is reasonable to conclude that for patients who are taking branded GA it may not always be necessary to stop therapy while attempting to become pregnant. Furthermore, among women who, in the opinion of their neurologist, require DMT coverage during pregnancy, GA therapy may be considered.^{30,31,33} □

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PRACTICE POINTS

- Because women with MS are no longer discouraged from becoming pregnant, there will be some early fetal exposures to disease-modifying therapies (DMTs).
- In specific situations (women with significant disease), continuation of DMT throughout pregnancy may be warranted.
- This study provides important information regarding the safety of branded glatiramer acetate early in pregnancy.

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