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1. ABSTRACT

Title

Biogen Multiple Sclerosis Pregnancy Exposure Registry

Keywords

Multiple sclerosis, pregnancy registry, Tecfidera, dimethyl fumarate

Rationale and background

Completed pregnancy registries in women with MS exposed to Avonex and Tysabri during their pregnancies have not suggested an increased risk of adverse pregnancy outcomes. The purpose of this registry was to assess pregnancy outcomes in women with MS exposed to other Biogen MS products. This registry initially included women exposed to Tecfidera (DMF) during pregnancy but was later expanded to include a Plegridy-exposed cohort and a DMT-unexposed cohort to provide an internal disease matched unexposed comparator.

Research question and objectives

Primary objective: to prospectively evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product.

Secondary objective: to prospectively evaluate pregnancy outcomes in women with MS who were unexposed to DMTs.

Study design

This was a prospective, observational registry designed to evaluate pregnancy outcomes in women with MS who were exposed to a registry-specified Biogen MS product during the eligibility window for that product or who were unexposed to DMTs.

Setting

Healthcare providers (HCPs) treating patients with MS were asked to report patients who became pregnant while being treated with a registry-specified Biogen MS product or who were unexposed to DMTs. Reporting of pregnancy exposures was voluntary. Pregnancies were reported as early as possible, ideally before prenatal testing had been performed.

Participants and study size, including dropouts

Participants had a diagnosis of MS with documented exposure to a registry-specified Biogen MS product or were unexposed to DMTs during the eligibility windows.

It was planned that each cohort would have a sufficient number of prospective pregnancies to observe 300 prospective outcome reports, where the outcome of the pregnancy was unknown at the time of the initial report.

Variables and data sources

Variables included pregnancy loss (elective/therapeutic terminations, spontaneous abortions, foetal deaths/stillbirths, ectopic/molar pregnancies), live births

(full-term/preterm), birth weight, head circumference, neonatal/perinatal/infant deaths, maternal deaths, and birth defects.

The Coordinating Centre (CC) collected data from participants and the participants' HCPs.

Results

Because of a lack of enrolment in the Plegridy and DMT-unexposed cohorts, results are from the Tecfidera cohort only. Of the 301 prospective participants without informative prenatal testing prior to enrolment, the mean (standard deviation [SD]) duration of gestational weeks of Tecfidera exposure was 5.1 (3.49) weeks. There were 308 foetuses (which included 7 sets of twins) and 289 known pregnancy outcomes. Of the 308 foetuses, there were 270 live births (87.7%), 15 spontaneous abortions (4.9%), 2 stillbirths (0.6%), and 2 elective/therapeutic pregnancy terminations (0.6%). There was 1 neonatal death (0.4%), which was not considered related to Tecfidera treatment. When including participants with informative prenatal testing prior to enrolment, there were 397 participants and the mean gestational weeks of Tecfidera exposure was 5.1 (SD 3.64) weeks. Of the 404 foetuses (including the 7 sets of twins) there were 379 known pregnancy outcomes with 360 live births (89.1%). There were no additional spontaneous abortions, stillbirths, elective or therapeutic pregnancy terminations, or neonatal deaths after live birth.

The rate of spontaneous abortion was 5.0% (95% confidence interval [CI]: 2.8, 8.1) in 301 participants without informative prenatal testing prior to enrolment and 3.8% (95% CI: 2.1, 6.2) in all 397 participants. Compared with data from the Avonex and the Tysabri pregnancy registries, the relative risk (RR) of spontaneous abortion was statistically significantly lower in participants exposed to Tecfidera in this study (Avonex: RR 0.41 [95% CI: 0.22, 0.76]; Tysabri: RR 0.44 [95% CI: 0.24, 0.81]). The rates of spontaneous abortion in the Avonex and Tysabri pregnancy registries were 9.18% and 8.51%, respectively, and were consistent with published background rates of 10% to 17% in the general population.

The proportion of live births and stillbirths/foetal deaths with adjudicator-confirmed major birth defects in participants without informative prenatal testing prior to enrolment was 3.7% per MACDP (95% CI: 1.8, 6.7) and 2.2% per EUROCAT (95% CI: 0.8, 4.7). The rate from all participants was 3.6% per MACDP (95% CI: 1.9, 6.1) and 2.2% per EUROCAT (95% CI: 1.0, 4.3). The rate of adjudicator-confirmed major birth defects was similar to the rate of birth defects in the EUROCAT database (RR = 0.94; 95% CI: 0.48, 1.87). Compared with the Avonex and Tysabri pregnancy registries, there was a lower risk of adjudicator-confirmed major birth defects in the Tecfidera group in this study; however, this was not statistically significant (Tecfidera versus Avonex: MACDP RR 0.58 [95% CI: 0.29, 1.17]; Tecfidera versus Tysabri: MACDP RR 0.71 [95% CI: 0.35, 1.46], EUROCAT RR 0.54 [95% CI: 0.23, 1.28]).

Discussion

There was no evidence of an increased rate of spontaneous abortions in participants exposed to Tecfidera in this study compared with other MS pregnancy registries that were potentially impacted by similar selection biases. Furthermore, the rates of

spontaneous abortion in this pregnancy registry were lower than published background rates in the general population and in studies including untreated pregnant women with MS.

The overall rate of adjudicator-confirmed major birth defects in this study was similar to the background rate in the EUROCAT database and lower (although not statistically significant) than the rates in the Avonex and Tysabri pregnancy registries, which had a more comparable population. Furthermore, most of the birth defects in this study were not temporally associated with Tecfidera exposure.

In conclusion, exposure to Tecfidera during pregnancy in participants with MS was not associated with an increased risk of spontaneous abortions or major birth defects compared with the general population or patients with MS exposed to Tysabri or Avonex.

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