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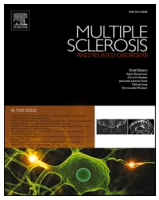

Original article

Safety evaluations of offspring breastfed by mothers receiving glatiramer acetate for relapsing multiple sclerosis

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ABSTRACT

Background: Although the relapse risk is increased after birth in women with relapsing multiple sclerosis (RMS), only a very few disease-modifying therapies (DMTs) are approved during breastfeeding. Glatiramer acetate (GA, Copaxone®) is one of three DMTs that can be used in breastfeeding. The real-world safety of Copaxone® in Offsprings of Breastfeeding and treated RMS pAtients (COBRA) study demonstrated that offspring parameters (hospitalisations, antibiotic use, developmental delays, growth parameters) were similar between offspring breastfed by mothers taking GA or no DMT (control) during breastfeeding. COBRA data analyses were extended to provide further safety data on the impact of maternal GA treatment during breastfeeding on offspring.

Methods: COBRA was a non-interventional, retrospective study using German Multiple Sclerosis and Pregnancy Registry data. Participants had RMS, gave birth and had GA or no DMT during breastfeeding. Offspring total adverse events (AEs), non-serious AEs (NAEs) and serious AEs (SAEs) up to 18 months postpartum were assessed. Reasons for offspring hospitalisations and antibiotic treatments were explored.

Results: Baseline maternal demographics and disease characteristics were similar between cohorts. Each cohort had 60 offspring. Numbers of offspring AEs were comparable between cohorts; total AEs: 82 (GA) vs 83 (control); NAEs: 59 vs 61; SAEs: 23 vs 22. AEs in both cohorts were diverse with no specific patterns. Duration of GA-exposed breastfeeding was 6 to >574 days for offspring with any AE. For all-cause hospitalisations, 11 offspring had 12 hospitalisations (GA cohort) and 12 control offspring had 16 hospitalisations. Most common reason for hospitalisation was infection: 5/12 (41.7%; GA) vs 4/16 (25.0%, control). Two out of 12 (16.7%) hospitalisations due to infection occurred during GA-exposed breastfeeding; the others occurred 70, 192 and 257 days after discontinuation of GA-exposed breastfeeding. Median (range) duration of GA-exposed breastfeeding was 110 (56 to ≥285) days for offspring hospitalised for infections and 137 (88–396) days for those hospitalised for other reasons. Nine offspring had 13 antibiotic treatments (GA cohort) and nine control offspring had 10 treatments. Ten out of 13 (76.9%) antibiotic treatments occurred during GA-exposed breastfeeding, of which four were primarily due to double kidney with reflux. Other antibiotic treatments occurred 193, 229 and 257 days after discontinuation of GA-exposed breastfeeding.

Conclusions: GA treatment of mothers with RMS during breastfeeding did not increase AEs, hospitalisations or antibiotic use in their offspring versus control offspring. These data support previous COBRA data that the benefit of maternal RMS treatment with GA during breastfeeding outweighs the potential, apparently low risk of untoward events, in their breastfed offspring.

1. Introduction

Disease-modifying therapies (DMTs) reduce relapse rates in relapsing multiple sclerosis (RMS) (Li et al., 2020). As women have a higher incidence of MS versus men (Magyari and Koch-Henriksen, 2022) and disease onset is more common in young people (D'Amico et al., 2018), the impact of pregnancy and postpartum on relapse rates in women with RMS is important (Langer-Gould et al., 2020; Hellwig et al., 2021;

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Varyté et al., 2020). DMT safety during all aspects of family planning requires careful consideration (Dobson et al., 2019; Wiendl et al., 2021).

Mothers and offspring benefit from breastfeeding. Breastfeeding mothers may have a reduced risk of ovarian and breast cancer, cardiometabolic diseases (Westerfield et al., 2018) and rheumatoid arthritis (Liao et al., 2009). Exclusive breastfeeding by mothers with RMS reduces postpartum relapses (Krysko et al., 2020). Benefits in breastfed offspring include improved cognitive functions (Westerfield et al., 2018; WHO, 2021), risk reduction for certain conditions (Westerfield et al., 2018) and decreased postpartum infections (Westerfield et al., 2018; WHO, 2021). Generally, breastfeeding should not be discouraged in favour of resuming DMTs in women with RMS (Thöne et al., 2017).

Based on European Summaries of Product Characteristics (SmPC), many DMTs are not advised during breastfeeding (Dobson et al., 2019; Wiendl et al., 2021; ECTRIMS/EAN, 2021). Terflunomide SmPC (2018), and Cladribine SmPC (2017) are contraindicated in breastfeeding. Several DMTs should not be used or should be discontinued during breastfeeding, i.e. Fingolimod SmPC (2020), Ocrelizumab SmPC (2018), Natalizumab SmPC (2016), Ozanimod SmPC (2020), Ponesimod SmPC (2021) and Siponimod SmPC (2020). For alemtuzumab, breastfeeding should be discontinued during each course and for 4 months following the last infusion of each course; although conferred immunity benefits of breastfeeding may outweigh risks of potential alemtuzumab exposure for the offspring (Alemtuzumab SmPC, 2018). For dimethyl fumarate, a decision should be made regarding discontinuing breastfeeding or treatment by considering breastfeeding benefit to the offspring versus treatment benefit for mother (Dimethyl fumarate SmPC, 2018).

Three DMTs for RMS are approved for women with RMS during breastfeeding, i.e. interferon-betas (IFN) (Interferon SmPC, 2008), glatiramer acetate (GA, Copaxone®) (Glatiramer SmPC, 2022) and ofatumumab (if clinically needed, starting breastfeeding a few days after birth or immediately after birth if ofatumumab was used up to the last few months of pregnancy) (Ofatumumab SmPC, 2021). (Pegylated) IFN treatment results in negligible human breast milk concentrations (Hale et al., 2012; Houtchens et al., 2022). Physicochemical properties and low oral absorption suggest that offspring exposure to GA via breast milk is negligible (GA SmPC, 2022). Several studies reported no significant impact of GA on offspring development during breastfeeding (Ciplea et al., 2020; Fragoso et al., 2010). A key study assessing GA effects on breastfed offspring was the real-world safety of Copaxone® in Offsprings of Breastfeeding and treated RMS pAtients (COBRA) study (Ciplea et al., 2022). In COBRA, several offspring parameters were evaluated for up to 18 months postpartum, i.e. annualised number of hospitalisations; proportion of offspring requiring hospitalisation; annualised number of antibiotic treatments; proportion of offspring requiring antibiotics; number and proportion of offspring with developmental delays; and offspring growth parameters. All parameters were comparable in offspring of mothers with RMS receiving GA during breastfeeding versus offspring whose mothers with RMS had no DMT during breastfeeding. Thus, maternal intake of GA during breastfeeding seemed to have no adverse impact on their offspring (Ciplea et al., 2022).

We extended these COBRA assessments by evaluating: type and frequency of adverse events (AEs) in breastfed offspring of mothers treated with GA; duration of GA exposure during breastfeeding; duration of GA exposure during pregnancy; reasons for any reported hospitalisations in both cohorts; and indications for events requiring antibiotics.

2. Methods

COBRA study details have been published previously (Ciplea et al., 2022).

2.1. Study design

COBRA was a non-interventional, retrospective study of real-world safety data of GA in breastfed offspring. Anonymised data were retrieved from the German MS and Pregnancy Registry (DMSKW) (Thiel et al., 2021) for 2011–2020.

2.2. Population

Key inclusion criteria for COBRA were RMS diagnosis, live birth and GA or no DMT treatment during breastfeeding. GA treatment during breastfeeding was defined as: GA during entire pregnancy and breastfeeding; or GA initiation during pregnancy and continuing during breastfeeding; or GA discontinuation during pregnancy and restarted before delivery and breastfed under GA treatment; or GA discontinuation during pregnancy and restarted during breastfeeding; or no GA during pregnancy and GA (re)started during breastfeeding. Mothers with no DMT during breastfeeding included those who: discontinued DMT during family planning; or discontinued GA in the first trimester; or had no past DMT treatment. Key exclusion criteria were breastfeeding mothers with other MS types, and those receiving other DMTs during breastfeeding.

Inclusion in the DMSKW was voluntary and informed consent was required for entry (Local Institutional review board: Ruhr-University Bochum, Registration number 18–6474-BR). COBRA did not require specific ethics committee/review board consent or ethical approval.

2.3. Data sources

The DMSKW collected data prospectively using standardised questionnaires in telephone interviews conducted by trained MS nurses or research associates (Thiel et al., 2021). Data were collected for each trimester after enrolment, for postpartum Months 1, 3 and 6, and yearly approximately on the offspring's birthday. Eighteen-month postpartum data were collected from interviews at 2 years.

Additional data were obtained from hospital discharge reports, clinical records, physician's letters, maternity logs and offspring medical check-up booklets. Hospitalisations and antibiotic uses were reported by the mother during interviews.

Remarks made in medical check-up booklets and non-serious illnesses were taken as AEs. Serious AEs (SAEs) were AEs which: resulted in death; were life threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability; caused congenital anomaly/birth defect.

2.4. Study endpoints

Total AEs, non-serious adverse events (NAEs) and SAEs up to 18 months postpartum in offspring born to mothers taking GA during breastfeeding versus controls (offspring breastfed by mothers not taking a DMT) were evaluated. Reasons for offspring hospitalisations and antibiotic treatments during breastfeeding were explored.

2.5. Data analyses

The GA cohort included mothers reporting at least 1 day of breastfeeding during GA treatment; controls were mothers receiving no DMT during breastfeeding. Maternal age at time of conception and offspring age at last follow-up were used to match control offspring with GA-cohort offspring. Breastfeeding was described as GA-exposed if the woman started GA treatment before weaning. Duration of GA-exposed breastfeeding was the time between GA start and weaning date.

Hospitalisation within the first year was defined as an overnight admission (yes/no), including hospitalisation directly after delivery (yes/no). Antibiotic use was defined as antibiotic treatment regardless of administration route (yes/no); for offspring with at least one antibiotic use in the first year, only systemic treatments were included, as in the reference population.

All statistical analyses were descriptive (including n, percentages, median and range) and were conducted using R version 4.0.2. Individual

AEs, NAEs, and SAEs were tabulated. All AEs were evaluated and their relevance to treatment were considered.

3. Results

3.1. Study population

Baseline maternal demographics and disease characteristics were similar between cohorts (Ciplea et al., 2022).

Median (range) duration of breastfeeding was 7.9 (0.2–22.4; GA) and 8.1 (0.2–28.2; controls) months. Numbers of offspring exclusively breastfed were 47 (78.3%; GA) and 49 (81.7%; control). Median (range) duration of GA-exposed breastfeeding was 7.0 (0.2–19.1) months; five offspring had <1 month of GA-exposed breastfeeding.

Overall, 120 offspring were followed up for up to 18 months postpartum; 57 (GA) and 56 (control) offspring had at least 12 months, and 29 (GA) and 45 (control) had at least 18 months of postpartum follow-up.

Table 1

3.2. Adverse events in the offspring (Table 1)

Total number of AEs of any type was similar between cohorts. For NAEs, 59 occurred in 38 offspring (GA cohort), and 61 were seen in 22 control offspring. Twenty-three SAEs occurred in 18 offspring (GA) and 22 were seen in 14 controls. AEs in both cohorts were diverse with no specific patterns, and AE types were similar between cohorts (data not shown).

Duration of GA-exposed breastfeeding was 6 to >574 days for offspring with any AE. Before starting GA-exposed breastfeeding, 11/82 (13.4%) any AE type, 4/59 (6.8%) NAEs, and 7/23 (30.4%) SAEs occurred in the offspring. Numbers (%) of overall AEs, NAEs and SAEs in the offspring occurring >3 months after discontinuation of GA-exposed breastfeeding were 11/82 (13.4%), 8/59 (13.6%) and 3/23 (12.5%), respectively.

Most GA-cohort offspring (52/60, 86.7%) were born to mothers receiving GA at some time during pregnancy. Other DMTs were used in five GA-cohort pregnancies i.e. fingolimod (n = 2), dimethyl fumarate (n = 2), and IFN (n = 1); however, one woman with an fingolimod-exposed pregnancy and one woman with a DMT-exposed pregnancy also started GA during pregnancy. Five GA-cohort pregnancies were not exposed to any DMT. For controls, 15/60 (25.0%) offspring were born to mothers who discontinued GA in the first trimester, as per study requirements. Median (range) of GA exposure during pregnancy was 66 (21–291; GA) and 29 (6–41; controls) days. Total duration of maternal GA exposure during pregnancy was 0–286 days for offspring with any AE type and those with NAEs. For offspring with SAEs, maternal GA exposure during pregnancy was 0–276 days. For controls, no mothers of offspring with any AE type had GA during pregnancy.

Table 2

Table 1
Summary of adverse events in offspring occurring during 18 months postpartum.

	GA cohort N = 60	Control cohort N = 60
Number of AEs (any type)	82	83
Number of NAEs	59	61
Number of NAEs per offspring, median (range)	1 (0–6)	1 (0–4)
Number of offspring with at least one NAE n (%)	38 (63.3)	22 (36.7)
Number of SAEs	23	22
Number of SAEs per offspring, median (range)	0 (0–3)	0 (0–5)
Number of offspring with at least one SAE, n (%)	18 (30.0)	14 (23.3)

All possible AEs (remarks in the medical check-up booklet) were included.
AE: adverse event; GA: glatiramer acetate; NAE: non-serious adverse event; SAE: serious adverse event.

Table 2
Summary of hospitalisations in offspring during breastfeeding.

Offspring outcomes	GA cohort N = 60	Control cohort N = 60
All-cause hospitalisations, n	12	16[a]
Number of offspring hospitalised, n	11[b]	12[c]
Hospitalisations due to an infection, n (%)	5/12 (41.7)	4/16 (25.0)
During GA-exposed breastfeeding	2/12 (16.7)	NA
Infection pattern	No	No
Total duration of GA-exposed breastfeeding for hospitalised offspring, range, days	56 to ≥285	NA
Due to infections	88 to ≥396	NA
Due to other reasons		
Total duration of maternal GA exposure during pregnancy, range, days	0–257	31[d]
Due to infections	22–259	
Due to other reasons		

[a] Of these 16 hospitalisations, 15 occurred at 12 months postpartum in offspring with a follow-up of up to 18 months; one hospitalisation occurred between 12 and 18 months postpartum in an offspring with a follow-up of at least 18 months.
[b] One offspring was hospitalised twice: once for medical supervision and once for *Respiratory syncytial virus* infection.
[c] One offspring was hospitalised four times for Hirschsprung's disease and one offspring was hospitalised twice, once for apnoea, and once for contusion capitis.
[d] One offspring.
GA: glatiramer acetate; NA: not applicable.

3.3. Offspring hospitalisations (Table 2)

3.3.1. GA cohort

Eleven offspring had 12 all-cause hospitalisations in the GA cohort (one offspring was hospitalised twice: once for medical supervision and once for *Respiratory syncytial virus* infection). Reasons for hospitalisation of these offspring were diverse with no particular pattern.

Five out of 12 hospitalisations (GA cohort) were due to diverse infections, i.e. pneumonia; *Escherichia coli* infection; influenza; *Respiratory syncytial virus* infection; and gastrointestinal infection (one offspring for each). Two of these five cases occurred during GA-exposed breastfeeding, constituting 16.7% (2/12) of all-cause hospitalisations. Three of the five infections occurred 70, 192 and 257 days after discontinuation of GA-exposed breastfeeding.

Duration of GA-exposed breastfeeding was 56 to ≥396 days for hospitalised offspring. There was no considerable difference in duration of GA-exposed breastfeeding (median, range) between offspring hospitalised for infection (110, 56 to ≥285 days) versus those hospitalised for other reasons (137, 88–396 days).

For all-cause hospitalised offspring, median (range) duration of maternal GA exposure during pregnancy was 36 (0–257) days. There was no difference in duration of maternal GA exposure during pregnancy (median, range) between offspring hospitalised for infection (49, 0–257 days) versus those hospitalised for other reasons (30, 22–259 days).

All but one of the mothers of hospitalised offspring were exposed to GA during the first trimester and during breastfeeding. Among these, one mother was also exposed to GA during the second and third trimesters.

3.3.2. Control cohort

Twelve control offspring had 16 all-cause hospitalisations (one offspring was hospitalised four times for Hirschsprung's disease; one offspring was hospitalised twice, once for apnoea, and once for contusion capitis). Hospitalisation reasons were diverse with no particular pattern.

Four hospitalisations were due to infections in the control offspring i.e. bronchitis; unknown infection; *Respiratory syncytial virus* infection; and pneumonia (one offspring for each).

Out of 16 all-cause hospitalisations in controls, only one offspring hospitalised due to infection was born to a mother who was exposed to GA for 31 days during the first trimester of pregnancy.

Table 3

3.4. Offspring antibiotic use (Table 3)

3.4.1. GA cohort

Thirteen infections required antibiotics in nine GA-cohort offspring; number of treatments/offspring: common cold (1/1); *E. coli* infection (1/1); bronchitis (2/2); urinary tract infection (4/1); purulent tonsilitis (1/1); conjunctivitis (3/2); otitis media (1/1). Three (23.1%) antibiotic treatments were topical; the rest were systemic.

Three (23.1%) antibiotic treatments occurred 193, 229 and 257 days after discontinuation of GA-exposed breastfeeding. Ten antibiotic treatments occurred during GA exposure while breastfeeding, among which four cases were primarily due to double kidney with reflux.

Excluding urinary tract infections due to double kidney with reflux, the rest of the infections treated with antibiotics were diverse with no specific pattern.

Duration of GA-exposed breastfeeding was 56 to >482 days for offspring receiving antibiotics. Duration of GA-exposed breastfeeding at the start of offspring antibiotic treatment was variable, median (range) 222 days (4–337) days.

Total duration of maternal GA exposure during pregnancy was 0–277 days. Of the nine offspring treated with antibiotics, seven (77.7%) were born to mothers exposed to GA at least during the first trimester of pregnancy.

3.4.2. Control cohort

Ten infections in nine control offspring required antibiotics; number of treatments/offspring: unknown infection (1/1); urinary tract infection (1/1); tonsilitis (1/1); conjunctivitis (2/2); influenza (1/1); otitis media (2/2); pneumonia (1/1); lung inflammation (1/1). One offspring had two infections requiring antibiotics (conjunctivitis and influenza).

Two (20%) antibiotic treatments were topical, the rest were systemic. Infections treated with antibiotics were diverse with no specific pattern.

Median (range) duration of maternal GA exposure during pregnancy was 28 (0–31) days. Three offspring (33%) treated with antibiotics were born to mothers exposed to GA during the first trimester of pregnancy.

Table 3
Summary of antibiotic treatments in offspring during breastfeeding.

Offspring outcomes	GA cohort $N = 60$	Control cohort $N = 60$
Number of antibiotic treatments, n	13	10
During GA-exposed breastfeeding	10	NA
Number of offspring treated with antibiotics, n	9[a]	9
Infection pattern	No	No
Total duration of GA-exposed breastfeeding for offspring treated with antibiotics, range, days	56 to ≥482	NA
At the start of antibiotic treatment	4 to ≥337	NA
Total duration of maternal GA exposure during pregnancy, range, days	0–277	0–31
In first trimester, n (%)	7/9 (77.8)	3/9 (33.3)

[a] One offspring was treated with four courses of antibiotics due to double kidney with reflux.

GA: glatiramer acetate; NA: not applicable.

4. Discussion

These additional safety evaluations of offspring up to 18 months postpartum in COBRA demonstrated that the number and types of AEs, NAEs and SAEs were similar in offspring of mothers treated with GA during breastfeeding versus those whose mothers had no DMT treatment during breastfeeding. Thus, these analyses expand on previous COBRA data (Ciplea et al., 2022), demonstrating that GA treatment of mothers during breastfeeding does not adversely affect breastfed offspring.

In the present COBRA data analysis, among the 82 AEs in the GA-cohort offspring, there were no AEs (NAEs or SAEs) that could be associated specifically with maternal GA-exposure during breastfeeding, due to one of the following reasons: 1) The AEs occurred more than 3 months after discontinuation of GA-exposed breastfeeding or GA-exposed breastfeeding did not start at the AE onset ($n = 22$); 2) The AEs also occurred in control offspring whose mothers were not exposed to GA during pregnancy or breastfeeding ($n = 48$); 3) The AEs were classified as congenital anomalies ($n = 3$); 4) The AEs were common conditions/illnesses in new-borns/offspring ($n = 9$, i.e. 3-day fever/Roseola, pyloric stenosis, retarded ankle growth, mononucleosis, shoulder inappropriate position, irritated skin, oral candidiasis, vascular dilatation right flank and strabismus) (Greiner et al., 2019; Frank et al., 2019). Moreover, none of these events were observed more than once, suggesting an absence of a trend that could potentially indicate a treatment relationship.

The incidence of all-cause hospitalisations of offspring of GA-exposed mothers in COBRA was comparable with control offspring and with the general infant population at the age of up to 12 months in North Rhine (Westphalia, Germany), where 18.7% of boys and 14.9% of girls were hospitalised for any reason at least once in the first year of life (Greiner et al., 2019). In COBRA, one of the most frequent reasons for hospitalisations was infection. This observation is also comparable with that in the general population of infants in North Rhine (Westphalia, Germany), where acute bronchitis was one of the three most common causes of hospitalisation during the first year of life (Greiner et al., 2019). Although the overall number of hospitalisations due to infections in COBRA was higher in the GA cohort versus controls (5/12 [42%] vs 4/16 [25%]), when excluding those with an onset beyond GA-exposed breastfeeding ($n = 3$), the frequency was lower in the GA cohort versus controls (2/12 [17%] vs 4/16 [25%]). COBRA data also suggest that there is no dose-dependant harmful effect as the duration of GA-exposed breastfeeding was similar in offspring hospitalised due to infection and for other reasons versus control offspring.

Regarding antibiotic treatments, the incidence in COBRA was the same in both cohorts (nine offspring, 15%). This incidence was lower than that reported for the general population of infants aged up to 12 months in North Rhine (Westphalia, Germany), i.e. 33.6% of boys and 29.6% of girls were treated with antibiotics at least once during their first year (Greiner et al., 2019). Although the overall number of antibiotic treatments in GA cohort was higher versus controls (13 vs 10), when excluding treatments with an onset outside of GA-exposed breastfeeding ($n = 3$) and those due to kidney disease with reflux in one infant ($n = 4$), the frequency was lower in GA cohort versus controls (6 vs 10). This finding also suggests no harmful effect of maternal GA exposure during breastfeeding on their offspring. Duration of GA-exposed breastfeeding at the start of antibiotic treatment was variable and similar to breastfeeding by the control cohort, thereby revealing no pattern of potentially harmful immunosuppressive effects.

It is important to emphasise that most offspring in the GA cohort in COBRA (86.7%) were born to mothers who were exposed to GA not only during breastfeeding but also at some point during pregnancy (mainly during first trimester), versus 25% of control offspring. Previous data showed that GA taken by women during pregnancy had no impact on congenital anomalies (Sandber-Wolheim et al., 2018; Kaplan et al., 2021), spontaneous abortions (Giannini et al., 2012) or birth weight (Herbstritt et al., 2016). In COBRA, the duration of GA exposure in

pregnancy in the GA cohort was approximately twice that of the control cohort. Although total maternal GA-exposure risk was higher in the GA cohort, there were no differences between cohorts in offspring safety outcomes.

Previous studies also reported no significant impact of GA on offspring outcomes. In offspring born to mothers who took GA during pregnancy and breastfeeding, no infections, signs of inadequate digestion or other ill effects were reported during or after breastfeeding (Fragoso et al., 2010). For women treated with either IFN or GA during pregnancy and breastfeeding, the offspring growth curves and body measurements during the first 12 months postpartum were consistent with national data (Ciplea et al., 2020). Previously reported COBRA data demonstrated no adverse impact of GA-exposed breastfeeding on offspring (Ciplea et al., 2022). Collectively, these data support the use of GA during breastfeeding.

The number of pregnancies/offspring in COBRA was relatively small, which is a potential limitation for data extrapolation to the wider population. However, COBRA group sizes should be put into perspective versus the estimated number of breastfeeding women with RMS in Europe. Based on epidemiology, a rough estimate of the number of women of childbearing age with MS is ~273,000 (GBD, 2019; Andersen and Magyari, 2020; Ziemssen et al., 2022). Moreover, pregnancy rate in women with RMS is 9.5% (Houtchens et al., 2018), with ~85% of pregnancies resulting in live births (Sandberg-Wolheim et al., 2018). Thus, ~22,000 mothers with MS give birth to live offspring. In the general population, 72% of mothers wish to breastfeed (Almas et al., 2016); therefore, ~15,000 mothers with MS may wish to breastfeed. One third of mothers with MS may experience a relapse postpartum (Vukusic et al., 2004), ~5000 women wishing to breastfeed may have a relapse. In COBRA, there were 118 women, which is ~0.8% (118/15,000) of the total number of women with MS, estimated as wishing to breastfeed. Thus, the GA cohort represents ~1.2% (58/5000) of the total patient pool estimated in Europe potentially experiencing a postpartum relapse. This compares favourably with phase 3 studies of DMTs used for European registration, which typically have a sample size of ~0.05% of the total patient pool. Thus, COBRA is valid in providing clinical evidence on the safety of GA-exposure of mothers during breastfeeding of their offspring in the first 18 months postpartum.

Overall, COBRA data have confirmed a lack of adverse safety outcomes in offspring of GA-treated mothers, followed-up for 18 months, i.e. no effects on AEs, hospitalisations and antibiotic use versus control offspring (Ciplea et al., 2022) or the general population (Greiner et al., 2019; Frank et al., 2019). These data add to the growing clinical evidence supporting GA use during breastfeeding, thereby reassuring mothers who need to take GA during pregnancy and breastfeeding. Several RMS treatment guidelines now recommend GA for use during breastfeeding (Dobson et al., 2019; Weindl et al., 2021).

Key strengths of COBRA are that this patient cohort is the largest of its kind, and the inclusion of a control group. COBRA has several limitations. As inclusion in the DMSKW is voluntary, there is a potential bias. The sample size in both cohorts was small and limited data were available for the 18-month follow-up. GA use during pregnancy and breastfeeding does not permit exclusive interpretation of the impact of GA during breastfeeding only. Due to the limited offspring number, only common AEs, not rare AEs, would be detected. Uncomplicated infections were not assessed as infections were only evaluated in offspring requiring hospitalisation and/or antibiotics.

5. Conclusions

This additional safety subanalysis of COBRA data demonstrated that breastfeeding of offspring by mothers with RMS taking GA did not increase AEs, hospitalisations or antibiotic use in the offspring versus those seen in offspring breastfed by mothers with RMS not on any DMT. These data support previously reported COBRA data, (Ciplea et al., 2022) that the benefit of maternal RMS treatment with GA during breastfeeding outweighs the potential, apparently low risk of untoward events, in their breastfed offspring. Further studies are needed to evaluate the effects of exposed breastfeeding on relapse risk.

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CRediT authorship contribution statement

Andrea I. Ciplea: Methodology, Validation, Data curation, Writing – review & editing. **Anna Kurzeja:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition. **Sandra Thiel:** Validation, Data curation, Writing – review & editing. **Sabrina Haben:** Software, Validation, Formal analysis, Data curation, Writing – review & editing. **Evelyn Adamus:** Methodology, Validation, Writing – review & editing. **Kerstin Hellwig:** Conceptualization, Methodology, Validation, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

Andrea I Ciplea has received speaker honoraria from Bayer HealthCare, Biogen GmbH, and Teva, as well as sponsorship for congress participation and travel grants from Teva.

Anna Kurzeja is an employee of Teva Pharmaceuticals Europe B.V.

Sandra Thiel has received speaker honoraria from Bayer HealthCare and Biogen GmbH, as well as payment for manuscript writing from HEXAL AG.

Sabrina Haben has nothing to disclose.

Evelyn Adamus has nothing to disclose.

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