MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Eighteen-month safety analysis of offspring breastfed by mothers receiving glatiramer acetate therapy for relapsing multiple sclerosis – COBRA study

Multiple Sclerosis Journal

2022, Vol. 28(10) 1641–1650

DOI: 10.1177/13524585221083982

Andrea Ines Ciplea, Anna Kurzeja, Sandra Thiel, Sabrina Haben, Jessica Alexander, Evelyn Adamus and Kerstin Hellwig

Abstract

Background: Safety data on disease-modifying therapies (DMTs) for relapsing multiple sclerosis (RMS) during breastfeeding are limited.

Objective: Assess safety outcomes for offspring breastfed by mothers undergoing glatiramer acetate (GA; Copaxone®) treatment.

Methods: This non-interventional, retrospective study used German Multiple Sclerosis and Pregnancy Registry data. Participants had RMS, a live birth, and received GA or no DMT during breastfeeding.

Results: GA cohort: 58 mothers/60 offspring; matched controls: 60 mothers/60 offspring; 86.7% (GA) and 25% (control) of offspring were born to mothers who had GA at some point during pregnancy. Maternal demographics and disease activity were comparable. Annualized number of hospitalizations was similar for breastfed offspring: 0.20 (95% confidence interval: 0.09–0.31; GA) and 0.25 (0.12–0.38, controls). Proportion of offspring requiring hospitalization was comparable between cohorts (18.33% vs. 20.00%). Annualized number of antibiotic uses was similar in both cohorts (0.22, 0.10–0.33 (GA) vs. 0.17, 0.06–0.27 (controls)) The proportion of offspring requiring antibiotics was 15.00% (both cohorts). More developmental delays were identified in controls versus the GA cohort (3 (5.36%) vs. 0). Growth parameters were comparable between cohorts.

Conclusion: Maternal intake of GA during breastfeeding did not adversely affect offspring safety outcomes assessed during the first 18 months of life.

Keywords: Relapsing–remitting multiple sclerosis, disease-modifying therapies, glatiramer acetate, offspring safety, pregnancy, breastfeeding

Date received: 28 June 2021; revised: 18 January 2022; accepted: 9 February 2022

Correspondence to:
K Hellwig
Department of Neurology, St. Josef Hospital – Katholisches Klinikum Bochum, Ruhr University Bochum, Gudrunstr. 56, 44791 Bochum, Germany.
kerstin.hellwig@rub.de

Andrea Ines Ciplea
Sandra Thiel
Sabrina Haben
Evelyn Adamus
Kerstin Hellwig
Department of Neurology, St. Josef Hospital – Katholisches Klinikum Bochum, Ruhr University Bochum, Bochum, Germany

Anna Kurzeja
European Medical Affairs, Teva Pharmaceuticals Europe B.V., Amsterdam, The Netherlands

Jessica Alexander
Teva Pharmaceutical Industries Ltd, West Chester, PA, USA

Introduction

Multiple sclerosis (MS) affects ~2.1 million individuals globally.[1] Relapsing MS (RMS) accounts for ~85% of all MS cases.[1] MS occurs at a two- to threefold higher incidence in women versus men, with disease onset most common during the reproductive years.[2,3]

Disease-modifying therapies (DMTs) extend time between MS relapses, thereby reducing accumulation of central nervous system damage and subsequent disability.[4] DMT use during pregnancy has been reviewed.[5–10] As up to 30% of mothers with MS may relapse within the first 3 months postpartum,[5] DMT safety during breastfeeding is important. Safety data on DMTs in breastfeeding mothers and their offspring are lacking. Thus, many mothers with MS have to opt between breastfeeding or re/starting DMTs postpartum.[11] Most DMTs for RMS are not advised during breastfeeding.[12,13]

Glatiramer acetate (GA; Copaxone®) is a large molecule, therefore, it is unlikely to be excreted in human milk. No significant effects of GA occurred on embryo-foetal development in rats and rabbits, or on offspring development in rats treated with GA from

day 15 of pregnancy throughout lactation.[14] A small, statistically significant reduction in bodyweight gain of offspring born to rats treated with GA during pregnancy and lactation was seen.[15] Of 5042 pregnancies in mothers treated with GA up to September 2014, outcomes were not at a higher risk of congenital anomalies versus the general population.[16] GA treatment during pregnancy was not associated with mean birth weight changes.[17] For individuals who may benefit from GA during breastfeeding for RMS, offspring safety remains important. Little is known about the effect of breastfeeding under GA treatment on offspring development and hospitalizations. German MS and Pregnancy Registry (DMSKW) data showed that body measurements, motor and language development, hospitalizations and antibiotic use, over 12 months postpartum, in offspring who were breastfed by mothers taking interferon-β, GA or both were consistent with national averages.[18]

COBRA aimed to assess offspring outcomes up to 18 months of development who were breastfed by mothers with RMS undergoing GA treatment versus offspring of mothers with RMS not exposed to any DMT during lactation. COBRA expands on observations of a previous combined analysis of DMSKW data in mothers taking either GA or interferon-β during lactation.[18] It provides data for GA separately and for longer duration follow-up, and, importantly, for the first time, relative to breastfed offspring of untreated mothers with RMS.

Materials and methods

Study design

COBRA was a non-interventional, retrospective study of real-world safety of Copaxone in Offsprings of Breastfeeding and treated RMS pAtients. Fully anonymized data were retrieved from the DMSKW for 2011–2020. Inclusion in this registry was voluntary and required informed consent (Local Institutional review board: Ruhr-University Bochum, Registration number 18-6474-BR). COBRA did not require ethical approval or ethics committee/review board consent.

The feasibility stage retrieved demographics and clinical characteristics of mothers with RMS. Based on sufficient numbers of mothers and key risk factors for negative birth outcomes, the confirmatory stage assessed safety outcomes of offspring breastfed by mothers undergoing GA treatment with offspring of mothers with RMS not exposed to any DMT during lactation (control), for 18 months postpartum.

Population

Specific inclusion criteria were: RMS diagnosis; live birth; breastfeeding under GA treatment; and breastfeeding with no DMT treatment (Supplementary Appendix). Breastfeeding mothers with MS other than RMS, or mothers treated with other DMTs during breastfeeding, were excluded. Thirty pregnancies in the GA cohort, but no control pregnancies, from COBRA were included in another analysis of the DMSKW.[18]

Exclusive breastfeeding was breastfeeding for at least 2 months without regular meal replacement by supplemental feeding.[19] Mothers reporting at least 1 day of breastfeeding during GA treatment were included in the GA cohort; mothers not receiving any DMT during breastfeeding were controls. Control offspring were matched to GA cohort offspring by maternal age at time of conception and offspring age at last follow-up. GA treatment was only with branded GA (Copaxone).

Data sources

Data were generated prospectively in the DMSKW by standardized questionnaires in telephone interviews in each remaining trimester after entry (months 1, 3 and 6 postpartum, yearly around the offspring's birthday; 18 months postpartum data from interviews at 2 years); see Supplementary appendix for further details.

Study endpoints

Maternal demographic and MS prognostic factors were documented (age, RMS disease duration, number of relapses in the 2 years preceding pregnancy and during pregnancy, number of steroid pulses during pregnancy, pregnancies under GA, GA exposure duration in pregnancy and during breastfeeding, follow-up duration).

Offspring safety was determined up to 18 months postpartum. Outcomes (Supplementary Appendix) included number and annualized number of hospitalizations and antibiotic treatments and the number and proportion of offspring requiring hospitalization and antibiotic treatments; number and proportion of paediatrician-assessed offspring developmental delay at 12 months (e.g. turning, attempt to grasp, sitting, turning towards voices, first words and standing; in Germany such mandatory check-ups are performed at approximately 1, 3, 6, 12 and 24 months postpartum); and growth parameters (body weight, body length and head circumference).

Data analyses

Statistical analyses were descriptive. Number of offspring with events, relative proportion of offspring with an event and 95% two-sided confidence intervals (CI) were calculated for binary outcome measures. Descriptive statistics of continuous outcome measures included *n*, mean, standard deviation and range. Analyses were conducted using R version 4.0.2. Five subgroup (>30 offspring required) analyses were planned (Supplementary Appendix).

Results

Maternal demographic and MS prognostic factors

The GA cohort had 60 offspring born to 58 mothers from 59 pregnancies (1 mother had twins; 1 mother had 2 pregnancies). The control cohort comprised 60 offspring born to 60 mothers from 60 pregnancies. During breastfeeding, mothers received either GA or no DMT (control). Overall, 120 offspring had up to 18 months of postpartum follow-up, 113 offspring had at least 12 months of postpartum follow-up (GA $n=57$; controls $n=56$) and 74 had at least 18 months of follow-up (GA $n=29$; controls $n=45$).

Baseline maternal demographic characteristics were similar (Table 1). Mean age at conception was similar between the cohorts. Both cohorts had the same number of preterm births. Median gestational age at study entry was higher in the GA cohort versus control. MS disease activity before and during pregnancy was similar (Table 1). Median number of relapses in the 2 years prior to conception and during pregnancy were similar for both cohorts.

In all, 86.7% of offspring were born to mothers treated with GA at some point during pregnancy versus 25% of controls whose mothers discontinued GA in the first trimester as per protocol.

A similar number of offspring were exclusively breastfed in both cohorts. Median breastfeeding duration was also similar between the cohorts. Median (range) duration of exposed breastfeeding was 7.0 (0.2–19.1) months (GA); 5 offspring had <1 month of exposed breastfeeding.

Offspring hospitalizations and antibiotic use

The annualized number of all-cause hospitalizations was similar for offspring in the GA cohort versus controls (Table 2). Five hospitalizations in the GA cohort (three occurred several months after GA-exposed breastfeeding had stopped) and four in the controls were due to infections (Table 2). The number and proportion of offspring requiring hospitalization were comparable for both cohorts (Table 2). For offspring with a longer follow-up of at least 18 months, the annualized number of hospitalizations and the number and proportion of offspring requiring hospitalization were also comparable between the cohorts (Table 2).

The number of antibiotic treatments was 13 in GA cohort (3 occurred several months after GA-exposed breastfeeding had stopped; 4 were in 1 infant due to double kidney disease with reflux) and 10 in controls (Table 3). Annualized number of antibiotic treatments was similar between cohorts. The number and proportion of offspring requiring antibiotic treatment were the same in both cohorts (Table 3). Infections requiring antibiotics were diverse and similar between cohorts (see footnote to Table 3). In offspring followed up longer, for at least 18 months, fewer offspring of mothers in the GA cohort had used antibiotics than controls (Table 3).

Excluding data from the 5 offspring who had <1 month of GA-exposed breastfeeding showed similar results to those described above (data not shown).

Offspring developmental delays

The number and proportion of offspring diagnosed with developmental delays in the GA cohort were lower versus controls (Table 4). No offspring in the GA cohort experienced a diagnosed developmental delay, while three control offspring (5%) had an event (motor delay $n=1$; language delay $n=1$; no detailed information $n=1$).

Offspring growth parameters

The average measurements for body weight, body length and head circumference were similar between cohorts (Table 5).

Subgroup analyses

Offspring of mothers treated with GA before and during pregnancy and during breastfeeding were compared with matched controls. The annualized number of hospitalizations was comparable between GA and control cohorts (Supplementary Table 1). The number and proportion of offspring requiring hospitalization were also comparable between cohorts (Supplementary Table 1). The annualized number of antibiotic treatments was higher in offspring from the GA cohort (Supplementary Table 2). The number and proportion of offspring requiring antibiotics were similar between

Table 1. Demographic and baseline characteristics of breastfeeding mothers with RMS.

Variable	GA cohort
	n = 58 mothers;
	n = 59 pregnancies;
	n = 60 offspring
		Control cohort
		n = 60 mothers/
		pregnancies/
		offspring

Mother's age at time of conception, mean (SD), years	33.1 (3.3)	32.9 (3.6)
Exclusive breastfeeding, *n* (%)	47 (78.3)	49 (81.7)
Preterm birth, *n* (%)	3 (5)	3 (5)
No completed vocational training, *n* (%)	0 (0)[a]	1 (1.7)[b]
University student, *n* (%)	1 (1.7)[a]	2 (3.3)[b]
Completed vocational training, *n* (%)	17 (28.3)[a]	28 (46.7)[b]
Completed university studies, *n* (%)	41 (68.3)[a]	26 (43.3)[b]
BMI at beginning of pregnancy, mean (SD), kg/m^2	25.1 (5.6)	24.5 (5.7)[c]
Gestational week of pregnancy at entry into the registry, median (range)	11.3 (1.0–39.3)	7.8 (3.6–38.3)
Disease duration at conception, mean (SD), years	4.6 (4.0)	6.8 (5.1)
Number of relapses in the 2 years preceding conception, median (range)	1 (0–5)	1 (0–6)
Number of relapses during pregnancy, median (range)	0 (0–2)	0 (0–2)
Number of steroid pulses during pregnancy, median (range)	0 (0–2)	0 (0–1)
GA exposure during pregnancy, *n* (%)	52 (86.7)	15 (25)
GA exposure duration during pregnancy, median (range), days	66 (21–291)	29 (6–41)
Duration of breastfeeding, median (range), months	7.9 (0.2–22.4)	8.1 (0.2–28.2)
Duration of exposed breastfeeding, median (range), months	7.0 (0.2–19.1)	NA
Follow-up duration, months, median (range)	13.3 (1.1–42.6)	24.7 (0.3–49.1)

BMI: body mass index; GA: glatiramer acetate (Copaxone®); NA: not applicable; RMS: relapsing multiple sclerosis; SD: standard deviation.
Parameters, for example, percentages and means, are calculated for mothers based on the number of offspring in the respective cohort (*n* = 60).
[a]*n* = 59.
[b]*n* = 57.
[c]*n* = 58.

the cohorts (Supplementary Table 2). No offspring in the GA cohort in this subgroup analysis had any diagnosed developmental delay, whereas two control offspring had an event (Supplementary Table 3). Body weight, body length and head circumference were similar between cohorts at birth, and at each time point up to 12 months (Supplementary Table 4).

The results of the subgroup analyses of offspring of mothers treated with GA before and/or during pregnancy and during breastfeeding compared with matched controls are shown in the Supplementary Appendix.

Discussion

COBRA demonstrated that offspring parameters (number and annualized number of hospitalizations and antibiotic treatments and the number and proportion of offspring requiring them, number and proportion of offspring with developmental delay, growth) of mothers with RMS treated with GA during breastfeeding were not adversely affected during 18 months postpartum as these parameters were comparable with offspring whose mothers with RMS were not treated with any DMT during breastfeeding. Most of the offspring parameters in the subgroup analyses of mothers treated with GA (before and during pregnancy and during breastfeeding; before and/or during pregnancy and during breastfeeding) were also similar to controls. The number of antibiotic treatments was higher in the subgroups in the GA cohort, which was due to one offspring receiving four antibiotic treatments due to urinary tract infections as a result of kidney disease with reflux.

GA is an immunomodulating agent,[15] raising potential concerns given the positive benefit of breastfeeding in immunology.[20] Hence, number and annualized number of and the number and proportion of offspring requiring hospitalizations and antibiotic treatments were included in COBRA. GA treatment during breastfeeding did not affect hospitalizations

Table 2. Number and annualized number of hospitalizations and number and proportion of offspring requiring hospitalization.

Group	Variable	GA cohort	Control cohort
Hospitalizations (number and annualized number)			
All enrolled offspring with up to 18 months follow-up GA cohort $n=60$; control cohort $n=60$	No. of events[a]	12[c]	15[d]
	Annualized no. of events (95% CI)	0.20 (0.09–0.31)	0.25 (0.12–0.38)
Offspring with at least 12 months follow-up GA cohort $n=57$; control cohort $n=56$	No. of events[a]	12	13
	Annualized no. of events (95% CI)	0.21 (0.09–0.33)	0.23 (0.11–0.36)
Offspring with at least 18 months follow-up GA cohort $n=29$; control cohort $n=45$	No. of events[b]	6	11
	Annualized no. of events (95% CI)	0.14 (0.05–0.28)	0.16 (0.06–0.36)
Hospitalizations (number and proportion of offspring)			
All enrolled offspring with up to 18 months follow-up GA cohort $n=60$; control cohort $n=60$	No. of offspring with event[a]	11	12
	Proportion of offspring (95% CI)	18.33 (9.52–30.44)	20.00 (10.78–32.33)
Offspring with at least 12 months follow-up GA cohort $n=57$; control cohort $n=56$	No. of offspring with event[a]	11	11
	Proportion of offspring (95% CI)	19.30 (10.05–31.91)	19.64 (10.23–32.43)
Offspring with at least 18 months follow-up GA cohort $n=29$; control cohort $n=45$	No. of offspring with event[b]	5	8
	Proportion of offspring (95% CI)	17.24 (5.85–35.77)	17.78 (8.00–32.05)

CI: confidence interval; GA: glatiramer acetate (Copaxone®); No.: number.
[a]In the period for 12 months postpartum.
[b]In the period for 18 months postpartum.
[c]In the GA cohort, there were a total of 12 hospitalizations. Five of these hospitalizations were due to infections; that is, pneumonia; *Escherichia coli* infection; influenza; *Respiratory syncytial virus* infection; gastrointestinal infection ($n=1$ infant for each). Three of these infections occurred 70, 192 and 257 days after discontinuation of GA-exposed breastfeeding.
[d]In the control cohort, there were a total of 16 hospitalizations. Four of these hospitalizations were due to infections; that is, bronchitis; unknown infection; *Respiratory syncytial virus* infection; pneumonia ($n=1$ infant for each).

and antibiotic treatments in the offspring in the first 18 months of life, indicating that infection risk was not elevated in these offspring. GA excretion in human breast milk is unknown.[14] Certain pharmacologic characteristics predict negligible drug concentrations in breast milk, including molecular weight, charge and protein binding.[21,22] GA has a large molecular weight (5000–9000 daltons),[14] is highly charged,[22] and has high protein binding;[15] therefore, GA is unlikely to diffuse into breast milk. Furthermore, GA will be subject to proteolysis after oral ingestion (hence subcutaneous administration of GA),[14] so gastrointestinal GA absorption will be negligible. Indeed, daily oral administration of up to 50 mg GA lacked clinical efficacy in MS.[23] These GA characteristics preclude clinically relevant transfer into milk, systemic absorption and pharmacologic effects in breastfed offspring. COBRA supports the lack of any clinically relevant exposure of offspring to GA from breast milk as no adverse effects on outcomes in offspring from mothers treated with GA were seen.

Breastfeeding benefits for mother and child are well recognized, and the World Health Organization advocates breastfeeding.[24] Maternal benefits include protection against certain diseases[25] and reducing risk of early postpartum MS relapses.[19,26] Offspring benefits include provision of a wide range of nutritional and immunologic components,[20] possible long-term protection from autoimmune diseases,[27] and possible improvement of childhood cognitive performance.[28] Thus, it is important that mothers on medication are allowed to breastfeed whenever possible, unless contraindicated or harmful for the mother and/or child.

DMTs are valuable in MS management.[4] DMT safety during lactation is important as MS relapses can occur within 3 months postpartum[5] and mothers might be

Table 3. Number and annualized number of antibiotic treatments and number and proportion of offspring requiring antibiotic treatment.

Group	Variable	GA cohort	Control cohort
Antibiotic treatments (number and annualized number)			
All enrolled offspring with up to 18 months follow-up GA cohort $n=60$; control cohort $n=60$	No. of events[a]	13[c]	10[d]
	Annualized no. of events (95% CI)	0.22 (0.10–0.33)	0.17 (0.06–0.27)
Offspring with at least 12 months follow-up GA cohort $n=57$; control cohort $n=56$	No. of events[a]	13	10
	Annualized no. of events (95% CI)	0.23 (0.10–0.35)	0.18 (0.07–0.29)
Offspring with at least 18 months follow-up GA cohort $n=29$; control cohort $n=45$	No. of events[b]	8	10
	Annualized no. of events (95% CI)	0.18 (0.05–0.48)	0.15 (0.06–0.24)
Antibiotic treatments (number and proportion of offspring)			
All enrolled offspring with up to 18 months follow-up GA cohort $n=60$; control cohort $n=60$	No. of offspring with event[a]	9	9
	Proportion of offspring (95% CI)	15.00 (7.1–26.57)	15.00 (7.10–26.57)
Offspring with at least 12 months follow-up GA cohort $n=57$; control cohort $n=56$	No. of offspring with event[a]	9	9
	Proportion of offspring (95% CI)	15.79 (7.48–27.87)	16.07 (7.62–28.33)
Offspring with at least 18 months follow-up GA cohort $n=29$; control cohort $n=45$	No. of offspring with event[b]	5	9
	Proportion of offspring (95% CI)	17.24 (5.85–35.77)	20.00 (9.58–34.60)

CI: confidence interval; GA: glatiramer acetate (Copaxone®); No.: number.
[a]In the period for 12 months postpartum.
[b]In the period for 18 months postpartum.
[c]In the GA cohort, 13 infections in 9 infants required antibiotics, these infections were (number of treatments/infants): common cold (1/1); *Escherichia coli* infection (1/1); bronchitis (2/2); urinary tract infection (4/1); purulent tonsilitis (1/1); conjunctivitis (3/2); otitis media (1/1). Among these 13 infections, 3 occurred 193, 229 and 257 days after discontinuation of GA-exposed breastfeeding and 4 (all in 1 infant) were caused by newborn double kidney with reflux that required surgery.
[d]In the control cohort, 10 infections in 9 infants required antibiotics, these infections were (number of treatments/infants): 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); inflammation of the lungs (1/1). One infant had two infections (conjunctivitis and influenza).

Table 4. Number and proportion of offspring with developmental delays.

Variable	GA cohort	Control cohort
No. of offspring with event[a]	0	3
Proportion of offspring (95% CI)[a]	0 (0.00–5.96)	5 (1.04–13.92)
No. of offspring with event[b]	0	3
Proportion of offspring (95% CI)[b]	0 (0.00–6.27)	5.36 (1.12–14.87)

CI: confidence interval; GA: glatiramer acetate (Copaxone®); No.: number.
[a]All enrolled offspring with a follow-up of up to 18 months postpartum, GA cohort $n=60$, control cohort $n=60$.
[b]All enrolled offspring with a follow-up of at least 12 months postpartum, GA cohort $n=57$, control cohort $n=56$.

counselled to restart medication and forego breastfeeding. Lack of DMT data during lactation means that mothers have to choose between MS treatment and breastfeeding.[11,13,29] Moreover, most DMTs for RMS are not recommended or are contraindicated during breastfeeding.[12]

Table 5. Offspring growth parameters at medical check-ups.

Parameter	U1 (birth)[a]	U2 (1st week of life)[b]	U3 (1st month of life)[c]	U4 (3–4 months of life)[b]	U5 (6–7 months of life)[d]	U6 (10–12 months of life)[e]
Body weight, mean (SD), g						
GA cohort	3443.78 (434.20)	3258.20 (416.21)	4462.02 (597.89)	6297.3 (724.12)	7872.25 (793.86)	9636.2 (980.75)
Control cohort	3317.88 (443.34)	3150.74 (404.95)	4269.26 (571.41)	6279.17 (865.93)	7914.95 (891.67)	9549.22 (1022.20)
Body length, mean (SD), cm						
GA cohort	51.72 (2.53)	51.86 (2.69)	55.14 (2.34)	62.23 (2.71)	68.25 (2.75)	75.27 (2.83)
Control cohort	51.46 (2.63)	52.11 (2.11)[f]	54.98 (2.29)	62.6 (2.81)	68.67 (2.72)	76.30 (3.67)
Head circumference, mean (SD), cm						
GA cohort	34.97 (1.47)[g]	34.86 (1.38)[h]	37.43 (1.34)	40.58 (1.27)	43.40 (1.38)[i]	46.07 (1.64)
Control cohort	34.89 (1.39)[j]	34.95 (1.17)[f]	37.13 (1.28)	40.82 (1.32)	43.40 (1.25)[k]	46.21 (1.47)

GA: glatiramer acetate (Copaxone®); SD: standard deviation; U: Untersuchung (English: medical examination).
[a]GA cohort, $n=60$; control cohort, $n=59$.
[b]GA cohort, $n=50$; control cohort, $n=42$.
[c]GA cohort, $n=51$; control cohort, $n=42$.
[d]GA cohort, $n=48$; control cohort, $n=43$.
[e]GA cohort, $n=50$; control cohort, $n=51$.
[f]$n=40$.
[g]$n=58$.
[h]$n=49$.
[i]$n=47$.
[j]$n=52$.
[k]$n=43$.

COBRA focused on the impact of maternal GA treatment, during breastfeeding, on the offspring. Data analyses were not adjusted for maternal demographic and clinical characteristics (age, disease duration, relapses) as these parameters were comparable between cohorts, and are unlikely to impact the offspring parameters reported. COBRA, the largest one of its kind in RMS, demonstrated no adverse effects on the offspring parameters evaluated in the observed timeframe, suggestive that GA treatment for RMS is compatible with breastfeeding. No clinically relevant differences in offspring growth parameters were seen between GA and control cohorts in COBRA; these results, along with the higher cumulative exposure to GA of mothers in the GA cohort, indicate lack of negative effect of maternal GA use on offspring safety. In a general population of children and adolescents from North Rhine-Westphalia, during the first year of life, percentages of offspring hospitalized at least once were 18.7% (boys) and 14.9% (girls),[30] and those receiving antibiotics at least once were 33.6% (boys) and 29.6% (girls).[30] COBRA findings were either comparable with (hospitalizations: 18% GA; 20% controls) or lower (antibiotic use: 15% in both cohorts) than these general population data.

The current observations support previous limited clinical data on GA safety during breastfeeding. Body weight, development (motor and language), hospitalizations and antibiotic use over 12 months postpartum in offspring ($n=74$) breastfed by mothers taking interferon-β, GA or both were comparable with national averages in Germany.[18] A small number of individual cases ($n=11$[31] in Brazil; $n=3$[32] in Germany) have reported normal development up to 6 and 12 months of age in offspring breastfed by mothers under GA treatment. Furthermore, there were no infections, signs of inadequate digestion or other significant ill effects suggesting relation to GA in breastfed offspring (during or after breastfeeding) born to mothers on GA during pregnancy and breastfeeding.[31] A key point in COBRA is that it compares two cohorts of patients with RMS (with GA treatment and with no DMT during breastfeeding).

COBRA observations are reassuring for mothers with RMS who want to be treated with GA and wish to breastfeed. Most mothers in the GA cohort were treated with GA at some point during pregnancy.[33] A planned subanalysis intended to evaluate offspring from mothers who only took GA during lactation. This group comprised only seven offspring and could not be evaluated. However, GA has demonstrated no increased risk of congenital anomalies when given during pregnancy,[16] no impact on spontaneous abortions[34] and no effects on birth weight.[17] COBRA expands these data, showing that continuing GA treatment during breastfeeding does not adversely

affect the offspring versus controls for the parameters and duration studied.

COBRA has several limitations. Although, it represents, to our knowledge, the largest cohort of its kind, the sample size was small and not all data on growth parameters and developmental delays were available for some offspring beyond 12 months and 29 (GA cohort) and 45 (control) offspring had longer than 18 months follow-up. The overlap of GA use during pregnancy and breastfeeding limits interpretation of GA effects on offspring solely during breastfeeding. The lack of adverse safety outcomes noted in offspring, followed-up for up to 18 months, of GA-treated mothers provides reassuring information for offspring of mothers taking GA during pregnancy and breastfeeding. Another limitation is that only common adverse events would have been observed due to the relatively small sample size. Rare negative effects cannot be excluded from present analysis, and more data have to be collected over time. Since participation in the DMSKW is voluntary, it is possible that potential bias could exist as relevant data may be missing. Outcomes among offspring lost to follow-up (46/120 had no data for the at least 18 months follow-up period) may differ from those with documented outcomes. Another limitation is that we cannot determine differences regarding the number of uncomplicated infections, as only infections requiring hospitalization and/or antibiotics were captured. However, the range of uncomplicated infections can be very wide in young offspring. It is difficult to capture and compare such infections as there are no standardized, objective parameters available and a paucity of published data.

Conclusion

COBRA demonstrated that offspring of mothers with RMS treated with GA during breastfeeding were not adversely affected during 18 months postpartum regarding the parameters studied as outcomes were comparable to offspring born to mothers with RMS and no DMT treatment during breastfeeding. These findings suggest that the benefit of maternal RMS treatment with GA during breastfeeding may outweigh the potential, apparently low risk of untoward events in breastfed offspring. COBRA data alongside that of another registry finding with GA[18] together with the unlikelihood of GA transfer into breast milk and negligible GA absorption by the gastrointestinal tract due to GA breakdown in the offspring gut may help support clinical decision-making. Larger and longer confirmatory studies are required to confirm the outcomes of COBRA. Offspring breastfed during maternal GA therapy should be monitored for possible adverse effects, as with all breastfed offspring whose mothers are receiving medication.

Acknowledgements

The authors thank all the participants of the German MS and Pregnancy registry as well as the referring neurologists and MS nurses. These analyses were a collaborative research project with Teva Pharmaceuticals. Medical writing support was provided by Jackie Phillipson of Ashfield Healthcare, part of UDG Healthcare, and was funded by Teva Pharmaceuticals.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: A.I.C. has received speaker honoraria from Bayer HealthCare, sponsorship for congress participation from Teva, and travel grants from Sanofi Genzyme, Teva and Novartis. S.T. has received speaker honoraria from Bayer HealthCare. S.H. and E.A. have nothing to disclose. K.H. has received travel grants from Biogen, Novartis and Merck and received speaker and research honoraria from Biogen Idec Germany, Teva, Sanofi Genzyme, Novartis, Bayer Health-Care, Merck Serono and Roche. A.K. is an employee of Teva Pharmaceuticals Europe B.V. and J.A. is a former employee of Teva Pharmaceutical Industries Ltd.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Funded by Teva Pharmaceuticals Europe B.V.

ORCID iD

Kerstin Hellwig https://orcid.org/0000-0003-4467-9011

Supplemental material

Supplemental material for this article is available online.

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