Topical Review

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Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis

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Abstract

For physicians who care for patients with multiple sclerosis (MS), the use of disease-modifying therapies (DMTs) during the conception period and pregnancy raises important safety considerations. All DMTs have potential adverse effects on fertility, pregnancy outcomes, and breastfed infants. Although physicians are reluctant to prescribe DMTs to MS patients who are contemplating having a family or are already pregnant, treatment can be warranted in those who have active disease. This review assembles the most current information on the reproductive safety of approved and emerging DMTs drawn from the literature and information supplied by the manufacturers.

Keywords

Disease-modifying therapies, pregnancy, multiple sclerosis, fertility, lactation

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Introduction

Despite years of experience, there is limited information regarding the safety of approved disease-modifying therapies (DMTs) on fertility, pregnancy, and lactation in patients with multiple sclerosis (MS). Even less is known about the reproductive safety of DMTs in late-stage development.

Safety information concerning drug use in pregnancy relies heavily on the United States Food and Drug Administration (FDA) pregnancy categories (Table 1). Since 1979, experts have advocated for the need to revise the pregnancy categories, citing that drugs are often assigned a pregnancy category based on incomplete data and in some cases no data at all.[1,2]

Parenteral DMTs of MS

Most data on the reproductive safety of parenteral DMTs are derived from case reports, prospective cohort studies, pregnancy registries, and safety databases maintained by manufacturers (Table 2).

Interferon beta 1b and 1a

The interferon betas (IFNβs) are pregnancy category C drugs.[3] There is no evidence of infertility or teratogenicity with the IFNβs; however, exposure during the first trimester was reported to cause a dose-dependent abortive effect in monkeys.[3] Two recent reports examined outcomes in human fetuses exposed to IFNβ. The first was a longitudinal, controlled cohort study that identified an increased risk of fetal loss and low birth weight in 23 pregnancies among 16 women exposed to IFNβ in the first trimester.[4] The second, a retrospective review of 41 in utero pregnancies from eight clinical trials reported 20 healthy full-term infants, one healthy premature infant, nine induced abortions, eight spontaneous abortions, one fetal death, and a congenital anomaly (hydrocephalus). Although not statistically significant, the miscarriage rate in the IFNβ-exposed pregnancies was higher than the rate expected in the US population.[5] In contrast, information on IFNβ exposure during pregnancy from the IFNβ-1a global safety database and three IFNβ pregnancy registries found that the rates of spontaneous abortions and major congenital anomalies with IFNβ align with the expected rates in the general population[6–9] (Tables 3 and 4). While transfer of IFNβ across the placenta is not significant, it is unknown if IFNβ enters breast milk.[3] However, gastrointestinal absorption of intact proteins by

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Table 1. US FDA categories for use of medications in pregnancy.

FDA category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have not demonstrated a fetal risk, but there are no adequate and well-controlled studies in pregnant women. Or Animal reproduction studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Or There are no animal reproduction studies and no adequate and well-controlled studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

US FDA: United States Food and Drug Administration.

breast-fed infants is unlikely. In the absence of any data, safe use of IFNβ while breastfeeding is undetermined.[3]

Glatiramer acetate

Glatiramer acetate (GA), pregnancy category B, does not affect fertility or cause teratogenic complications.[3,10] Knowledge of GA exposure in human pregnancy comes from a retrospective analysis of 215 pregnancies included in the manufacturer's safety database between 1996 and September 2002. There were five single cases of congenital abnormalities (finger anomaly, adrenal cyst, cardiomyopathy, urethrostenosis, anencephaly) and one birth defect (failure to thrive). The number of live births, miscarriages, and therapeutic terminations aligned with the general population[10] (Table 3); GA does not cross the placental barrier and is considered probably compatible with breastfeeding.[11] Given that GA is an amino acid polymer, it is unlikely to be absorbed intact across an infant's gastrointestinal mucosa.

Natalizumab

Natalizumab (pregnancy category C) is a humanized monoclonal IgG4 antibody that targets the α4-integrin receptor.[12] Animal studies evaluated the effects of natalizumab on fertility and pregnancy outcomes. In guinea pigs, reductions in pregnancy rates were observed at 30 mg/kg (36-fold the human clinical dose). No adverse effects on male fertility were reported.[13] Human uterine epithelium and embryonic tissue express α_4-integrin receptors. Theoretically, natalizumab could interfere with implantation and embryonic development by inhibiting cell-cell interactions, but neither has been reported.[14] Cardiovascular complications are possible through inhibition of α_4 integrins involved in the development of the epicardium. However, in preclinical studies, no cardiac abnormalities were reported in monkeys treated with doses up to 30 mg/kg.[14]

Information on pregnancy outcomes is limited. In the natalizumab MS and Crohn's disease clinical trial program, 41 pregnancies were reported. These pregnancies resulted in 12 full-term births, 10 ongoing pregnancies, six spontaneous abortions, and 13 with unknown outcomes, which align with expected outcomes in the US population.[15] In the gastroenterology literature, 102 pregnancies exposed to natalizumab were prospectively followed. There were 55 (53.4%) live births, no stillbirths, 27 (26.2%) elective terminations, 21 (20.4%) spontaneous abortions, and no congenital malformations.[16,17] Interim results from the Tysabri Pregnancy Exposure Registry (TPER) were recently published (Table 4). Fetal malformations were observed in 23 pregnancy outcomes in 21 women. Compared with historical controls, there were no significant differences in the rate of fetal malformations.[18] Natalizumab crosses the placenta in the second trimester and is secreted in human milk in small amounts.[12] Although it is unlikely that natalizumab would be absorbed intact across the gastrointestinal mucosa, safe use in nursing mothers is not established.[11,12]

Mitoxantrone

Mitoxantrone (pregnancy category D) causes amennorhea.[3,19] In animals, growth retardation and premature births were reported.[20] In mitoxantrone MS clinical trials, nine

Table 2. Reproductive safety of parenteral DMTs approved for patients with RRMS.

Drug effect on	Interferon-β (1a, 1b)	Glatiramer acetate	Mitoxantrone	Natalizumab
Fertility	Menstrual irregularities in monkeys	No adverse effects in rats	No adverse effects in rats and rabbits	Reduced fertility in guinea pigs; increased abortions in monkeys
	No well-controlled studies in humans	No well-controlled studies in humans	Chemotherapy induced amenorrhea in humans	No well-controlled studies in humans
Teratogenicity	No malformation in monkeys	No malformation in rats and rabbits	Fetal growth retardation in rats; no teratogenic effects in rabbits Potential human teratogen based on MOA	No adverse effects in monkeys; small reduction in guinea pig pup size
Pregnancy reports (published)	Avonex Pregnancy Registry (*n*=226) Betaseron Pregnancy Registry (*n*=69) Rebif Global Database (*n*=425)	Glatiramer global database (*n*=215)	(*N*=9) in MS trials (*N*=5) in case reports	Natalizumab Pregnancy registry (*N*=341)
Placental transfer	Unlikely IFNβ-1a MW= ~22,500 Da IFNβ-1b MW= ~18,500 Da	Unlikely MW=5000–9000 Da	Limited MW=514 Da	Yes, in guinea pigs and monkeys
Secreted in breast milk	Unknown	Unknown/unlikely	Yes	Yes; IgG4 in second and third trimester
Nursing	Not recommended	Discuss potential risk with patients	Not recommended	Not recommended
Waiting time off drug before conception	Not reported	Not reported	6 months	3 months
FDA pregnancy class	C	B	D	C

DMTs: Disease-modifying therapies; RRMS: relapsing–remitting multiple sclerosis; MOA: mechanism of action; MS: multiple sclerosis; MW: molecular weight; IFNβ: interferon beta; US: United States; Interferon beta 1b (Betaseron®), Bayer HealthCare Pharmaceuticals Inc., Montville, NJ; Interferon beta 1a (Avonex®), Biogen Idec Inc., Cambridge, MA; Interferon beta 1b (Extavia®), Novartis Pharmaceuticals Corp., East Hanover, NJ; Interferon beta 1a (Rebif®), EMD Serono Inc., Rockland, MA; Glatiramer acetate (Copaxone®), Teva Pharmaceuticals USA, Kansas City, MO; Mitoxantrone (Novatrone®), EMD Serono Inc., Rockland, MA; Natalizumab (Tysabri®), Biogen Idec Inc., Cambridge, MA.

Table 3. Postmarketing surveillance databases: Exposure to DMTs in pregnant patients with RRMS.

Postmarketing database	# Pregnancies (evaluable outcomes)	# Live births	# Spontaneous abortions	# Still births	# Terminated pregnancies	Observations
Rebif (IFNβ-1b) Global Safety Database 1998–2009 Sandberg-Wollheim et al. 2011[6]	425[a]	328	49	4	39	Four of 328 live births were associated with congenital anomalies. The rate of spontaneous abortions (11.5%) was consistent with the US population.
Copaxone (glatiramer acetate) 1996–2003 Coyle et al. 2003[10]	215	155	43	1	9	In 155 live births, there were five single cases of congenital anomalies (finger anomaly, cardiomyopathy, urethrostenosis, anencephaly, adrenal cyst) and one birth defect (failure to thrive). The rate of spontaneous abortions (20%) was consistent with the US population.

DMTs: Disease-modifying therapies; RRMS: relapsing–remitting multiple sclerosis; IFNβ: interferon beta; US: United States; [a]: prospectively collected.

Table 4. Multiple sclerosis pregnancy registries with disease-modifying therapies.

Pregnancy registry	# Pregnancies (evaluable outcomes)	# Live births	# Spontaneous abortions	# Still births	# Terminated pregnancies	Observations
Betaseron (IFNβ-1b) 2006–2009 Coyle et al. 2010[7]	69	59	8	2	0	Three of 59 live births were associated with a birth defect. The rate of spontaneous abortions (11.5%) was consistent with the US population.
Avonex (IFNβ-1a) 2003–2009 Foulds et al. 2010[8]	226	193	28	1	4	Fifteen of 193 live births were associated with at least one major or two minor defects. The rate of malformations was not increased or overrepresented. The rate of spontaneous abortions (12.4%) was consistent with the US population.
Rebif (IFNβ-1b) 2002–2007 US Pregnancy Registry	34	NR	2	1	NR	SAEs occurred in 10/32 (31.3%). The rate of spontaneous abortions (6.3%) was consistent with the US population.
Tysabri (natalizumab) 2007–Nov. 2011 Cristiano et al. 2012[18]	334	286	34	1	13	Twenty-three of 234 live births were associated with malformations. As this is an interim analysis, the rate of major malformations has not been calculated. The rate of spontaneous abortions (11.2%) is consistent with the US general population.

IFNβ: interferon beta; US: United States; SAEs: severe adverse effects that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect.

pregnancies were reported resulting in six healthy infants, two pregnancies with unknown outcomes, and one ongoing pregnancy.[21] Patients should be instructed not to become pregnant while taking mitoxantrone and for at least six months after discontinuation.[11] Placental transfer of mitoxantrone is limited; however, it is secreted in milk and contraindicated when breastfeeding.[3,22]

Oral small molecules

Two small molecules (fingolimod and teriflunomide) are approved for the treatment of relapsing forms of MS. Unlike proteins, small molecules have the potential to be absorbed by the digestive tract and widely distributed. Their potential for placental transmission is greater than for recombinant proteins (Table 5).

Fingolimod

Fingolimod (pregnancy category C) is an oral sphingosine 1-phosphate (S1P) receptor modulator that prevents the egress of lymphocytes from lymph nodes.[23] In rats, exposure to fingolimod caused a slight decrease in pregnancies; however, the effect of fingolimod on human fertility is unknown.[23–25] Fingolimod is teratogenic in rats.[23,26] Congenital abnormalities, including persistent truncus arteriosus, were reported.[25,26] This finding is not unexpected given that S1P receptors are involved in vascular development during embryogenesis. Limited information exists regarding the safety of fingolimod in pregnancy. In the fingolimod MS clinical trial program, 34 pregnancies resulted in 13 healthy infants, one infant with a tibia malformation believed to be unrelated to fingolimod, five spontaneous abortions, nine elective abortions, and six ongoing pregnancies.[27] A pregnancy registry is ongoing. When treatment is stopped, elimination of fingolimod takes approximately two months because of its long half-life. Patients should use effective contraception and wait at least two months following discontinuation before attempting conception.[23,26] Fingolimod crosses the placenta and is secreted in breast milk; use in nursing mothers is not recommended.[23]

Dimethyl fumarate

Fumaric acid esters (pregnancy category pending approval) have been used for the treatment of psoriasis for more than 50 years, primarily in Germany.[28] Despite a long history of use, there is little information on reproductive safety. Available studies on teratogenicity are conflicting. In preclinical studies conducted with Fumaderm® (dimethyl fumarate and ethyl hydrogen fumarate), there was no evidence of teratogenicity.[29] In guinea pigs, exposure to fumaric acid 1% (about 400 mg/kg twice per day) did not cause adverse effects on reproduction or fetal growth.[30,31] However, in rats, dimethyl fumarate at doses ≥ 178 mg/kg resulted in embryotoxicity and teratogenicity with malformations observed in organs, coccyx, and skull bone.[32] In an observational study

Table 5. Reproductive safety of oral small molecules in patients with RRMS.

Drug effect on	Fingolimod	Cladribine	Dimethyl fumarate	Teriflunomide	Laquinimod
Fertility	Decreased pregnancies in rats	Potential male infertility in monkeys	Not reported in animals	No evidence of impaired fertility in male and female rats	Not reported in animals
	Not reported in humans	Not reported in humans	Not reported in humans	Not reported in humans	Not reported in humans
Teratogenicity	Fetal malformations in rats	Fetal malformations in mice and rabbits	Fetal malformations in rats	Fetal malformations in rats and rabbits	Fetal malformations in rats, but not in rabbits, with roquinimex
	Not reported in humans	Not reported in humans	Not reported in humans	Not observed in humans	Not reported in humans with roquinimex
Pregnancy reports (published)	(*N*=59) in MS clinical trials	(*N*=19) in MS clinical trials (*N*=1) case report in hairy cell leukemia	(*N*=15) case series in psoriasis patients with fumaric acid	(*N*=53) with teriflunomide in safety database; (*n*=11) with teriflunomide in clinical trials	Not reported
Placental transfer	Yes	Unknown	Not reported	Yes (in animals)	Not reported
Secreted in breast milk	Yes	Unknown/Possible	Not recommended	Unknown	Not reported
Nursing	Not recommended	Not recommended	Not reported	Not recommended	Not reported
Waiting time off drug before conception	12 months	6 months	Not reported	Suspend teriflunomide, initiate 11-day course of cholestyramine 8 g three times daily to decrease blood levels to < 0.02 mg/l. Verify in two separate tests at least 14 days apart.	Not reported
FDA pregnancy class	C	D	Not assigned	X	Not assigned

RRMS: relapsing–remitting multiple sclerosis; MS: multiple sclerosis; FDA: United States Food and Drug Administration; Fingolimod (Gilenya™), Novartis Pharma AG, Stein, Switzerland; Cladribine oral (investigational) Merck Serono, Frenches Forest, Australia; Cladribine (Leustatin®), Centocor Ortho Biotech Products LP, Raritan, NJ; Dimethyl fumarate (investigational) Biogen Idec Inc., Cambridge, MA; Teriflunomide (investigational) Genzyme a Sanofi Company, Cambridge, MA; Leflunomide (Arava®), Sanofi-Aventis U.S. LLC, Bridgewater, NJ; Laquinimod (investigational), Teva Pharmaceuticals USA, Kansas City, MO.

of 15 psoriasis patients exposed to fumaric acid during pregnancy, there was one spontaneous abortion, one stillbirth, and no evidence of embryotoxicity or teratogenicity.[33] It is unknown if dimethyl fumarate crosses the placenta or is secreted in breast milk. Use of dimethyl fumarate during breastfeeding is not recommended.[28,29]

Teriflunomide

Teriflunomide (pregnancy category X) is contraindicated in pregnant women and women of childbearing potential who are not using reliable contraception.[34] Teriflunomide causes teratogenicity throughout the period of organogenesis in rats and rabbits with high incidences of craniofacial, axial, and appendicular skeletal defects. Studies assessing the risk of male-mediated fetal toxicity have not been conducted; however, teriflunomide can be detected in human semen. Due to gastrointestinal reabsorption, following discontinuation the plasma concentration of teriflunomide can take eight months or longer (up to two years) to drop below 0.02 mg/l, a level considered safe for reproduction. If a patient, or a potential father, on teriflunomide wants to conceive or becomes pregnant, the drug should be stopped and an accelerated elimination procedure initiated. Cholestyramine 8 g every eight hours for 11 days is administered. If cholestyramine 8 g three times a day is not well tolerated, the dose can be decreased by 50%.[34] Early experience with teriflunomide in pregnant MS patients comes from the Teriflunomide Multiple Sclerosis Oral (TEMSO) study and the Teriflunomide Pharmacovigilance Database. In the TEMSO study, 11 pregnancies were reported resulting in six terminated pregnancies (all in women receiving teriflunomide), four miscarriages (one in the placebo group and three in the teriflunomide group), and one healthy newborn by a patient who was treated with teriflunomide for 31 days of her pregnancy.[35] The Teriflunomide Pharmacovigilance

Database is a retrospective collection of pregnancy outcome data from 53 pregnant MS patients with direct (n=41) or indirect exposure (n=12) to teriflunomide. The 53 pregnancies resulted in 17 healthy newborns, 19 terminated pregnancies, nine miscarriages, and eight ongoing pregnancies. Eight of the 10 women with direct exposure to teriflunomide who delivered healthy newborns underwent the recommended drug elimination protocol in the first trimester. No structural or functional defects were reported.[36] Teriflunomide crosses the placenta and is detected in rat milk following a single oral dose. It is unknown if teriflunomide is secreted in human milk.[34] Until further information is available, breastfeeding is not recommended.

Laquinimod

Laquinimod (pregnancy category pending approval), a second-generation quinoline-3-carboxamide analog structurally related to roquinimex, is under investigation for relapsing forms of MS.[37,38] Animal studies demonstrated fetal malformation in rats, but not in rabbits, exposed to roquinimex and other quinoline compounds.[37,39] A theoretical concern with quinoline-3-carboxamides is their potential anti-angiogenic effect.[38] However, no case of fetal vascular malformations due to quinoline-3 carboxamide exposure has been reported. Until reproductive safety data are available, women of childbearing potential are advised to use effective contraception and lactating mothers should not breastfeed.[40]

Cladribine

Parenteral cladribine (pregnancy category D) is indicated for the treatment of hairy cell leukemia and lymphoma.[41,42] Recently, the development of oral cladribine for the treatment of MS was discontinued. Cladribine causes suppression of rapidly dividing cells, including testicular cells. Men are advised to not father children while taking cladribine and for at least six months after its discontinuation.[41,42] In animals, cladribine is teratogenic at all stages of utero development, but there is no evidence of teratogenicity in humans.[41–43] Data on cladribine exposure in human pregnancy are limited.[43,44] A successful pregnancy following administration of cladribine to a patient with hairy cell leukemia was reported.[45] It is not known if cladribine crosses the placenta or is secreted in breast milk. However, given its molecular weight (~286), there is the possibility that cladribine crosses the placenta and is secreted in milk.[11,41] Cladribine use while breastfeeding is not recommended.[11]

Monoclonal antibodies

Several IgG1 monoclonal antibodies (mAbs) show promise in MS treatment. (Table 6). IgG1 antibodies do not cross the placenta in the first trimester, protecting the infant from exposure during the crucial period of organogenesis, from 18 to 50 days after conception.[46] However, they efficiently cross the placenta in the third trimester and could have immunological effects on the fetus.

Alemtuzumab

Alemtuzumab (pregnancy C) is a humanized IgG1 monoclonal anti-CD52 antibody that is FDA approved for B-cell chronic lymphocytic leukemia (B-CLL) and in late-stage development for relapsing MS.[47] No fertility complications have been reported; however, alemtuzumab may cause reversible infertility in males because of inactivation of mature sperm.[48] Since B-CLL affects mainly elderly patients, alemtuzumab reproductive toxicity studies have not been conducted. Alemtuzumab crosses the placenta (second and third trimesters) and enters breast milk. Breastfeeding should be avoided for at least three months after stopping treatment.[43,49]

Anti-CD20 monoclonal antibodies

Rituximab is no longer being evaluated for the treatment of MS; however, two second-generation anti-CD20 mAbs are in phase 3 trials: ocrelizumab and ofatumumab. Rituximab (pregnancy category C), a chimeric IgG1 anti-CD20 mAb, is FDA approved for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and other select autoimmune diseases.[50] Experience with rituximab may provide some guidance on the reproductive safety of second-generation anti-CD20 mAbs. In animal studies, infertility and congenital malformations were not observed; however, a dose-dependent depletion of B-cells was observed in fetuses.[50,51] Case reports of rituximab treatment during pregnancy suggest that it does not result in serious effects on newborns.[52] However, women are instructed to avoid pregnancy while taking rituximab. Due to its long half-life, it was proposed that treatment be stopped 12 months before conception (although this proposal may be overly conservative).[52] Rituximab likely crosses the placental barrier and is secreted in milk in small amounts; breastfeeding is not recommended.[50,53]

Ocrelizumab (pregnancy category pending approval) is a humanized IgG1 CD20 mAb in clinical trials for relapsing and progressive forms of MS. To date, no information has been published on its reproductive safety. Ofatumumab (pregnancy category C), a human IgG1 anti-CD20 mAb, is FDA approved for refractory chronic lymphocytic leukemia and is being investigated in MS. Fertility studies with ofatumumab have not been conducted. In monkeys, fetal malformations were not observed with 100 mg/kg ofatumumab, the highest dose tested.[54,55] The same instructions for rituximab use in women of childbearing potential apply to ofatumumab and ocrelizumab.

Table 6. Reproductive safety of monoclonal antibodies in patients with RRMS.

Drug effect on	Alemtuzumab	Rituximab	Ofatumumab	Ocrelizumab	Daclizumab
Fertility	No studies conducted in animals	No adverse effects in monkeys	Not reported	No published data	No studies conducted in animals
	Potential risk of reversible infertility in males	No adverse effects in humans	Not reported	No published data	No studies conducted in humans
Teratogenicity	No studies conducted in animals	No evidence in monkeys	No evidence in monkeys	No published data	No evidence in monkeys
	No studies conducted in humans	Transient B-cell depletion in offspring	Decreased weight and transient B-cell depletion in offspring	No published data	Increased prenatal loss vs. placebo
Pregnancy reports (published)	Not reported	(*N*=253) in clinical and postmarketing database	Not reported	Not reported	Not reported
Placental transfer		Crosses the placenta in monkeys			
	IgG1 crosses the placenta in second and third trimester	IgG1 crosses the placenta in second and third trimester	IgG1 crosses the placenta in second and third trimester	IgG1 crosses the placenta in second and third trimester	IgG1 crosses the placenta in second and third trimester
Secreted in breast milk	Has not been studied	In monkeys	Not reported	Not reported	Secreted in low concentration in monkeys
Nursing	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Waiting time off drug before conception	6 months	12 months	12 months	Not reported	4 months
FDA pregnancy class	C	C	C	Not assigned	C

RRMS: relapsing–remitting multiple sclerosis; FDA: United States Food and Drug Administration; Alemtuzumab (Campath®), Genzyme Corporation, Cambridge, MA; Rituximab (Rituxan®), Genentech, Inc. South San Francisco, CA; Ofatumumab (Arzerra®), Glaxo Group Limited, Greenford, Middlesex, United Kingdom; Ocrelizumab (investigational) Roche, Basel, Switzerland; Daclizumab (Zenapax®), Hoffman-La Roche, Nutley, NJ.

Daclizumab

Daclizumab (pregnancy category C), a humanized IgG1 monoclonal anti-CD25 antibody, was FDA approved in 1997 for the prevention of renal allograft rejection and is being investigated for the treatment of MS. Fertility studies have not been conducted with daclizumab.[56] Fetal malformations were not observed with daclizumab in monkeys, although there was an increase in prenatal loss. Women of childbearing potential are advised to use effective contraception while taking daclizumab and for four months after discontinuation.[56] Very low concentrations of daclizumab are secreted in breast milk of lactating monkeys. Breastfeeding is not recommended during treatment.[57]

Summary

Unfortunately, no DMT is proven to be safe during pregnancy or while breastfeeding. Despite limited data on their reproductive risks, small molecules are considered to carry unacceptable risks due to their potential to cross the placenta and be secreted in breast milk. Risks for some small molecules are considered established (mitoxantrone, teriflunomide, and cladribine) whereas others remain suspected (fingolimod, dimethyl fumarate, and laquinimod). In contrast monoclonal antibodies do not cross the placenta during organogenesis and therefore are unlikely to be teratogenic; however, they can cross the placenta during the second and third trimesters, and use of these drugs late in pregnancy could have immunological consequences for the unborn infant. Although monoclonal antibodies could be secreted in breast milk, because they are proteins that require parenteral administration, it is unlikely that they will be absorbed intact by breastfed infants. Similar reasoning applies to the IFNs; however, ongoing use of IFNs in women planning pregnancy may be relatively contra-indicated because of their possible abortifacient property. In women who need to continue DMTs, GA appears to be the only available treatment that can be used with relative safety. While treatment with GA can be continued during pregnancy, there is always the risk of unforeseen adverse events. It is hoped that this review will be a useful source

for clinicians who are faced with the challenge of counseling their patients about the potential risks and benefits of continuing with, or abstaining from, treatment before, during, and after pregnancy.

Conflict of interest

Dr Cree has received personal compensation for consulting from Biogen Idec, EMD Serono, Genzyme, Novartis, Sanofi-Aventis, and Teva Neurosciences.

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