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Brittany Edralin
University of Tennessee, Knoxville, mlp358@vols.utk.edu

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Medication use while breastfeeding with multiple sclerosis: A systematic literature review

Brittany Edralin

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ABSTRACT

Background: Multiple sclerosis (MS) is an immune-mediated disease where neurons in the central nervous system are demyelinated. Prevalence among women is twice as much as men and usually develops during childbearing years, causing concerns about the effects drug therapy may have on breastfeeding infants.

Objective: To systematically review evidence regarding medications used to treat MS and to determine which are likely to be safe for use during breastfeeding.

Methods: Web of Science and Pubmed databases were searched for publication dates between 1950 and March 2016. Prescribing information on medications and reference lists of included articles were also searched. Each study was assessed using predetermined inclusion and exclusion criteria. Data were extracted based on study design, sample size, intervention, outcome measures, and results.

Results: Literature indicates that interferon β, glatiramer acetate, prednisolone, methyl prednisolone, and immunoglobulin, are likely safe for use when breastfeeding, as medication levels present in human milk were insignificant and/or no adverse effects in infants were observed. However, natalizumab, mitoxantrone, alemtuzumab, fingolimod, and teriflunomide were all shown to be excreted in either human or animal milk. While no adverse effects on infants have been reported with these drugs, prescribing information does not recommend use while breastfeeding. It is unknown whether dimethyl acetate is excreted in either human or animal milk. Until more data are gathered, it is not recommended to use while breastfeeding.

Conclusion: Overall, research on medication transfer through breast milk and adverse effects on infants is very limited. While there are some options for mothers with MS who wish to breastfeed, more research needs to be done to explore more options for them.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated disease where neurons in the central nervous system (CNS) are demyelinated.[1] Demyelination occurs when macrophages and cytotoxic T cells cause chronic inflammation that subsequently causes damage to the myelin sheath that surrounds nerve cells. As a result, lesions form in the CNS, impeding the conduction of electrical impulses that control muscle groups.[2] It is unknown exactly what causes this process to occur, however, it has been speculated that there may be more than one mechanism.[1] MS is manifested by numerous and diverse symptoms which develop depending on the location of the lesions. Symptoms may be physical, with impairment of vision, speech, and/or muscle coordination, and may also affect cognitive function, causing issues such as memory loss and/or depression.[2] Treatment is usually administered through immune-mediating drugs to help reduce relapses and slow progression of the disease.[1]

There are multiple types of MS.[1-3] The most common type is *relapsing-remitting*, which is when an individual suffers from decline after a period of recovery, but then improves and is symptom-free for a period before another relapse occurs.[3] Symptoms usually develop over several days, stabilize, and then improve within weeks.[1] Other forms of MS include *primary progressive*, *secondary progressive*, and *progressive-relapsing*.[1,2] In *primary progressive* and *secondary progressive* MS, neurological function deteriorates over time. However, in *primary progressive*, they experience no early relapses, while those with *secondary progressive* usually start with initial relapses before steady decline eventually occurs. *Progressive-relapsing* MS is a rare form where the symptoms of the disease steadily worsen with no relapses but with acute exacerbations.[2] MS commonly first occurs in early adulthood, between the ages of 20 and 30.[1,2]

About 2.3 million people have been diagnosed with this condition, with women being affected twice as frequently as men.[1,2,4]

Because multiple sclerosis mostly affects women after the age of 20 and because this coincides with the childbearing years, maternal and infant health outcomes need to be considered. Historically, women with multiple sclerosis were discouraged from becoming pregnant.[5] However, recent studies show that pregnancy does not exacerbate the long-term results of MS and may also be beneficial in reducing the frequency of relapses.[2,5,6] Research has also shown that breastfeeding is not associated with postpartum relapses and may actually help reduce the frequency of postpartum relapses, especially in women who are not on disease-modifying therapy.[6-8]

The World Health Organization recommends that most infants are breastfed exclusively (receive no other foods or fluids) for 6 months after birth for optimal health benefits such as protection against infectious diseases and improvement of cognitive development.[9] Breast milk also provides adequate nutrition for appropriate growth and development of their organs.[10] Importantly, breastfeeding may also be beneficial to maternal health, providing decreased risk for certain cancers and promoting optimal child spacing.[9] These benefits extend to mothers with MS.[2] Exclusive breastfeeding induces hormonal changes which in turn produce anti-inflammatory results.[2] Decreased inflammation prevents destruction of the myelin sheath, so the nerve cells are able to conduct electrical signaling normally.[2,11] Despite these benefits for both mother and infant, when a lactating mother is taking disease-modifying medications, drug transfer through breast milk must be considered. While some medications are safe, not all are, and the decision must be made by carefully balancing the risk/benefit ratio between disease treatment and the benefits of breastfeeding.[5]

Drug exposure through breast milk consumption is an important area of study, as infants who are exclusively breastfed depend on this food source for all of their nutrient needs.[10] If medications or other possible xenobiotic substances are in the milk in significant concentrations, they might interact with the physiological processes occurring in the infant's body and inhibit growth or cause abnormalities.[10,12] When studying the transport of these medications through the cells where milk is produced, which are mammary alveolar cells, many factors have to be considered including molecular weight, ionization, and carrier proteins.[10,12] In addition to the characteristics of the medication compound itself, another major factor is plasma or serum levels in the mother.[10] If she has high levels of the medication in her system, there is a chance that it will be high in milk as well, depending on the dosage administered and the ability of the mother's body to absorb and/or metabolize it.[10] These factors should be taken into consideration when a mother who needs drug therapy is contemplating breastfeeding.

While there are several systematic reviews on use of medications during pregnancy and the postpartum period in women with multiple sclerosis, there are none that focus solely on use of these medications during lactation.[13-15] The purpose of this review is to explore the literature on disease-modifying medications used in treatment of multiple sclerosis and consolidate the information in a comprehensive analysis of which medications are likely to be safe and which are contraindicated for use during breastfeeding.

METHODS

Search Strategy

Web of Science and PubMed databases were searched to identify original research studies published between 1950 and March 2016. These dates were chosen because in 1950, after

World War II, scientists began making breakthroughs in research, contributing to much of what is known about MS today.[16] The following keywords were used in both database searches to find relevant articles: "multiple sclerosis", "drug", "breastfeeding", "breast feeding", "lactation", "interferon", "glatiramer acetate", "natalizumab", "mitoxantrone", "alemtuzumab", "fingolimod", "teriflunomide", "dimethyl fumarate", "prednisolone" and "intravenous immunoglobulin". These medication names were determined by reviewing the medications page of the National Multiple Sclerosis Society's website.[17] All medication names are the generic version. The reference lists of identified review articles cited by other articles at least five times in original research articles, were searched to identify additional studies related to drug therapy for MS that were not discovered in the original key word search. In addition, prescription information on all medications found on the National Multiple Sclerosis Society's website was examined.[17]

Study Selection

Inclusion criteria included 1) having lactating females (human or animal) as subjects, 2) evaluation of an MS drug therapy intervention, and 3) reported outcomes of serum, plasma, or breast milk levels of the medication (maternal or infant) and/or report of side effects in infants. Exclusion criteria included 1) not an original research article and 2) not available in English. Articles were either retrieved directly from the Web of Science or Pubmed databases or were obtained from the interlibrary loan service of the University of Tennessee, Knoxville. The titles and abstracts of all articles were reviewed and compared against the inclusion and exclusion criteria. If no abstract was available or if the abstract was lacking sufficient information, the full article was examined. Citations in review articles were used to identify additional original

research studies that met the inclusion criteria. Articles were excluded if they were a duplicate of a previously-selected publication.

Data Extraction

Data were extracted regarding study design, sample size, intervention, outcome measures, and results. Outcomes of interest included levels of drugs excreted in milk and effects on breastfed infants.

RESULTS

The preliminary search using the identified key terms yielded 69 unique articles (38 from Web of Science; 31 from Pubmed). However, 33 of these were review articles, 6 were not available in English, 2 were commentaries, and 1 article was no longer available on the website (the only identified location of the article). The remaining 21 articles were reviewed for relevant outcome measures. Only 5 of these 21 evaluated breast milk levels of the medication and/or report side effects in infants. When reference lists of review articles were searched, 4 additional articles meeting the inclusion criteria were identified. These 9 articles, along with specific characteristics of each, are outlined in the Table. In addition to these 9 articles, prescription information was included for all medications identified on the National Society of Multiple Sclerosis website. This review categorizes the medications by type: injectable, infused, oral, and other.

Table. Summary of studies found on disease-modifying medications used for multiple sclerosis during lactation

Author(s)	Medication Evaluated	Sample Size	Outcome Measure
Hale et al.[18]	Interferon β	6	Medication level in breastmilk

Salminen et al.[19]	Glatiramer acetate	13	Side effects on infants
Fragoso et al.[20]	Glatiramer acetate	11	Side effects on infants
Baker et al.[21]	Natalizumab	1	Medication level in breastmilk
McKenzie et al.[22]	Prednisolone	7	Medication level in breastmilk
Cooper et al.[23]	Methylprednisolone	1	Medication level in breastmilk
Greenberger et al.[24]	Methylprednisolone	3	Medication level in breastmilk
Strijbos et al.[25]	Methylprednisolone	1	Medication level in breastmilk
Achiron et al.[26]	Immunoglobulin	79	Side effect on infants

Injectable Medications

Interferon Beta

Interferons are a class of proteins that are usually produced by lymphocytes when bacteria, viruses, or other parasites invade the body, and these proteins are believed to down-regulate the autoimmune response that occurs in MS.[18] The mechanism of action is not yet fully understood.[18] However, it is known that these proteins take part in anti-proliferative and immunomodulatory actions, meaning that they inhibit cell growth and alter the immune response.[18] It is the most commonly used immunomodulatory drug for treatment of MS.[19] There are three major types of interferons, but only interferon β has been used in the clinical setting for MS.[18] Due to its large molecular size, a characteristic that has shown to decrease drug transfer to milk, interferon β was researched by scientists to determine if its use could be continued in patients with MS who desire to breastfeed.[10] The medication has to be injected subcutaneously three times per week and therefore may present a significant burden to a mother trying to breastfeed her infant.[27]

In one observational study[18], six women with MS volunteered to collect their breast milk and allowed it to be analyzed. The subjects had been receiving a dose of 30 μg of interferon β intramuscularly every week for at least one month. The first sample collected served as the control. Mothers collected samples of their milk at 1, 4, 8, 12, 24, 48, and 72 hours post-injection. Each breast was pumped for 12 minutes with an electric breast pump to assure collection of both fore and hind milk. The samples from each breast were pooled and then sent to the lab.

For their method of measurement, an enzyme-linked immunosorbent assay, there was a limit of detection of 20 pg interferon β/mL.[18] Many of the specimens obtained had concentrations of interferon β-1a below this level. Each mother provided 8 samples, however, the medication was not detected in all of these, indicating variability between and among mothers. For example, no medication was detected in any of the 8 samples from one mother, while it was detected in 2 of the 8 samples from another mother, and in 3 of the 8 samples from another mother. Therefore, some mothers had more samples to compare against than others. The detectable amounts ranged from 32.9 pg/mL to 179 pg/mL. Using the maximum level detected (179 pg/mL), the researchers calculated the relative infant dose and found that it would only be 0.006% of the maternal dose. At the end of the study, none of the subjects reported any adverse effects in their infants while breastfeeding.[18] The authors suggest that for doses that are typically provided for those with MS, the levels of interferon β-1a that are passed through human milk are likely to be inconsequential and are unlikely to cause harmful effects on breastfeeding infants.

Since the subjects were not supervised when pumping their milk, there might have been some inaccuracy in the data.[18] The mothers were in control of when they obtained their samples and may not have followed the desired schedule, possibly skewing the results by having

significantly different levels of drug in their breast milk than the other mothers during the same time interval. A limitation of this study is that it followed a small sample of women over a short period of time, inhibiting the generalizability of the study. The strongest study design that would provide stronger evidence would be a randomized control trial (RCT) conducted over a longer period.[28] However, this is not plausible as breastfeeding is a personal choice and it is unethical to tell a mother to breastfeed or not. The article states that this is the first study that has attempted to quantify the transfer of interferon β into breastmilk.[18] Since no other study on this topic was found in the literature search, this is likely to be the only evidence available that provides any support that interferon β can be used while a mother is breastfeeding. However, it is important to note that the prescribing information for interferon β reports that is not recommended.[29]

Glatiramer acetate

The mechanism by which glatiramer acetate, a synthetic polymer, acts to treat MS is not completely understood.[30] However, it is speculated that it binds to major histocompatible molecules in order to produce secretion of anti-inflammatory cytokines.[30] Glatiramer acetate can be administered either every day, at 20 mg/mL, or three times per week, at 40 mg/mL.[31] This frequency may be an important consideration for those wanting to breastfeed. In this systematic search, no studies were found that measured glatiramer acetate concentrations in breast milk. Therefore, to gain more insight into the possible safety of using this medication while breastfeeding, two retrospective evaluations of women with MS who were treated with glatiramer acetate during pregnancy and the effect on their infants were reviewed.[19,20]

In one case series, thirteen women with MS who were taking glatiramer acetate as treatment were asked to come in for a systematic follow up after their pregnancies. However, the authors only report on infant feeding mode for 12 women, with 2 breastfeeding (one for 2

months and the other for 6 months), six breastfeeding for less than 2 weeks, and the remaining 4 not breastfeeding at all. It is unknown why there was nothing reported for the 13th mother. At the end of the study, the researchers reported observing no drug-related outcomes for the mothers or infants and none of the mothers who breastfed reported any unusual behavior or activity from their infants.[19] However, the authors did not report when the follow-up occurred, therefore, it is not possible to determine length of exposure and/or timing of observation of the infants.

In another case series, conducted in Brazil, eleven women with clinically diagnosed MS and their children were retrospectively assessed.[20] These women had received glatiramer acetate consistently for at least 7 months of their pregnancies. Of these eleven women, nine breastfed their infants, and did so for an average of 3.6 months. No infections, developmental issues, or other significant negative effects were observed in the children by their mothers. While there was one case of neonatal infection, it was not considered to be drug induced.[20]

While these case series did not specifically survey medication levels in milk, the effect on exposed infants is something to take into consideration when determining drug safety. Since no injurious symptoms were exhibited by the breastfed children, there is some evidence that glatiramer acetate, if passed through human milk, is likely not excreted at high enough levels to cause complications. However, there are limitations to these studies since they are only case series and cannot prove cause and effect and maternal observation of infant behavior could introduce bias.[28] Neither study had a control group that allowed for comparison against the women and infants exposed to glatiramer acetate. In addition, review of prescribing information indicates that glatiramer acetate is not recommended while breastfeeding.[31]

Infused Medications

Natalizumab

Natalizumab is a recombinant humanized IgG_4 monoclonal antibody and is categorized as a selective adhesion molecule inhibitor.[21] Natalizumab acts to inhibit activation, migration, and function of leukocytes in areas of inflammation by blocking them from attaching to the α4-integrin molecule. This helps decrease the frequency of relapses in inflammatory diseases such as MS.[21] Natalizumab is typically infused at 300 mg intravenously for about one hour, every four weeks.[32] Breastfeeding women may find this relatively low frequency attractive. However, the limited research on this medication inhibits the ability to assess the safety of its use during breastfeeding.

Only one article was found that examined the transfer of natlizumab into breast milk.[21] In this case report, a 28-year old female with MS started drug therapy while breastfeeding her infant. She was given the typical dosage of 300 mg IV which was infused over 1 hour every four weeks. Milk samples were collected 3 weeks before treatment was initiated and then collected every day after her first dosage over the following 50 days. She received a second dosage on day 29. The levels of natalizumab in the milk were then measured, allowing the researchers to see how long the drug would be excreted in milk over the course of about two weeks.

The noncompartmental pharmacokinetic method of assessment, utilized in this study, is capable of detecting levels of natalizumab at or above 0.25 µg/mL.[21] During the first 13 days after the first infusion, the concentration of natalizumab in the milk was undetectable. However, on day 14, levels were detected at a concentration of 0.33 µg/mL. From day 15 to 28 levels fluctuated between 0.339 and 1.008 µg/mL, but remained relatively low. Interestingly, after day 29 the concentration began to rise daily, reaching a maximum amount of 2.83 µg/mL on day 50. This may indicate that natalizumab levels in breast milk continue to escalate.

Two methods were used to calculate the relative infant dose (concentration-time curve and breast milk concentration).[21] The area under the concentration-time curve estimated the relative infant dose to be 1.74%, while the average concentration in milk calculation resulted in an estimate of 5.3%.[21] The authors report that, generally, a dose less than 10% is considered safe for a breastfeeding infant.[21] Therefore, both of the doses calculated above were well below this safe level. However, the researchers were concerned that levels of natalizumab in milk would continue to escalate to possibly toxic levels past the 50 day mark. While these results indicate that breastfeeding might be safe to do for a certain amount of time, it should be considered that continuous use of natalizumab could cause increased amounts to be transferred through milk as the drug collects in the milk ducts.[21] A long-term study, and ideally an RCT, would be beneficial in exploring the concerns raised by this case report, as a case report is generally considered to be a weak study design.[28] The prescribing information reports that natalizumab can pass through milk, but that it is unknown whether or not it is harmful for infants.[32] Interestingly, there is no statement of contraindication of use during breastfeeding, only the emphasis on mothers who are planning to breastfeed communicating with their physician that they are on this medication.[32]

Mitoxantrone

Mitoxantrone is a cytotoxic, antineoplastic agent and immunomodulatory drug.[33] It is usually given once every three months for about two to three years through an infusion that takes about five to 15 minutes to administer.[34] This relatively low frequency may be especially attractive to breastfeeding women. The mechanism of action includes activating macrophage-mediated suppression of B-cell, T-helper, and T-cytotoxic lymphocyte function. Mitoxantrone also inserts into DNA which prevents DNA strands from coming together, slowing the cell-cycle progression. Levels of mitoxantrone have been found to remain in tissue for extended periods of

time, suggesting that it is slow to be eliminated from the body. For example, an autopsy found measurable levels in tissue from a patient who had received the dosage up to 272 days before death.[33]

Searching the databases using the relevant key terms yielded no research evaluating mitoxantrone secretion in breast milk. Related reviews were examined for sources to determine current recommendations.[13-15] The prescribing information provided by the Food and Drug Administration (FDA) reports evidence that mitoxantrone is excreted in breast milk and that high concentrations (18 ng/mL) of the drug have been found in milk 28 days post-infusion.[34]

Although data are extremely limited on this drug, the likelihood that mitoxantrone is slow to be eliminated from the body could be an indication that this drug is not the safest to use while breastfeeding. Elevated levels in the maternal plasma are likely to be mirrored in breast milk and could result in adverse effects for a breastfed infant.[10] In fact, the FDA does not recommend that women take mitoxantrone and breastfeed at the same time.[34] Women attracted to the relatively low frequency of dose, who are considering breastfeeding, should be informed about the FDA recommendation and should not breastfeed if using this medication.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody, for which the mechanism of action is not completely understood.[35] However, there is some indication that it targets cell surface proteins on lymphocytes and monocytes and is connected to T-cell migration and co-stimulation. Alemtuzumab eliminates $CD52^+$ tumor cells and is involved in the initiation of apoptosis.[35]

No literature was found evaluating the excretion of alemtuzumab into breast milk. Prescribing information does not provide information on whether it is transferred into human milk, however, similar compounds have shown to be able to do so.[36,37] Prescribing information

also states that alemtuzumab is excreted in the milk of lactating mice.[36,37] The lack of information on this drug could be that it is relatively new, compared to the other disease-modifying drugs used for multiple sclerosis.

Alemtuzumab is administered through an IV infusion over two hours three times per week for about 12 weeks.[36] Therefore, it is likely to present a significant burden to a mother with a young infant, regardless of infant-feeding mode. Due to the frequency of the dosage and the lack of knowledge about adverse effects on infant health, mothers with multiple sclerosis should probably not breastfeed while on this medication.

Oral Medications

Fingolimod

Fingolimod is a sphingosine 1-phosphate receptor modulator.[38] It works by first being phosphorylated and then binding to a series of different molecules to ultimately reduce inflammation and aid in the repair of the central nervous system. Fingolimod may also be able to help treat chronic infections.[38] It is recommended to be taken orally once a day.[39]

Searching the databases yielded no studies on fingolimod use during breastfeeding or measurement of fingolimod expression in human milk. However, prescribing information indicates that fingolimod has been detected in the milk of lactating rats.[40] In treated animals, levels of the drug have found to be 2-3 times higher than levels found in the plasma of the mother.[39] There appears to be no publicly available information regarding adverse effects on infants, however, both the FDA and EMA (European Medicines Agency) recommend that women who are being treated with fingolimod do not breastfeed or that they discontinue therapy if they choose to breastfeed.[39,40]

Teriflunomide

Teriflunomide is a high affinity inhibitor of dihydroorotate dehydrogenase which is a key enzyme in the production of pyrimidine.[41] Pyrimidine is needed by fast proliferating cells, like lymphocytes, to meet DNA, lipid, and glucose metabolism needs. Teriflunomide is unique, however, in that it is selectively active and only targets proliferating lymphocytes.[41] This is beneficial because there is no concern that it will attack non-malignant cells, causing other adverse symptoms. Teriflunomide tablets (7mg or 14mg) should be taken daily, with the dose depending on severity of disease.[42]

Similar to the previous three drugs, no research was found on teriflunomide and transfer during lactation. However, prescribing information reveals that teriflunomide has been detected in the milk of lactating rats after receiving a single dose.[42,43] Therefore, it is advised that mothers should either cease breastfeeding or stop taking teriflunomide, depending on the how significant the drug is to the mother's health.[42,43]

Dimethyl fumarate

Dimethyl fumarate is an oral therapeutic agent that reduces both disease activity and progression in *relapsing-remitting* MS, as it functions through multiple pathways.[44] For example, dimethyl fumarate is able to inhibit immune cells and may have anti-oxidant properties that help prevent damage to the brain or spinal cord.[44] This medication begins with 240 mg capsules taken twice a day for seven days, but then increases to a dosage of 240 mg twice a day.[45]

Information on dimethyl fumarate is extremely limited.[45,46] It is unknown whether dimethyl fumarate is excreted in breast milk. The prescribing information does not provide any information on milk transfer, in humans or other animals.[45,46] This may be because this medication is also still relatively new, having been released three years prior to this review.[47]

Other Medications

Corticosteroids

Corticosteroids are often used to quickly mitigate relapses.[1] They can be administered either orally (prednisolone) or intravenously (methylprednisolone) for management of exacerbations.[17,48,49] The most common treatment used for MS is a high-dose intravenous administration of methylprednisolone, which has potent anti-inflammatory and immunosuppressive effects over three to five days.[17,23] This intravenous dose is typically followed by an oral dosage of prednisolone that gradually tapers off over the course of ten days to six weeks.[49] A high oral dose may also be used if intravenous administration is not desired or if it is contraindicated.[49] The dosage and frequency of administration varies, however, depending on the severity of the disease.[48,49]

It appears that the transfer of steroids into breast milk has been studied to a much greater extent than other MS therapies. For example, the earliest study found in this review was published in 1975 and analyzed prednisolone levels in the milk of seven lactating mothers for 48 hours after an oral dosage of 5mg.[22] Milk was expressed via breast pump at different intervals, at which point it was analyzed by liquid scintillation using oxidation. The results showed that the highest level of prednisolone in the milk was found in the first sample from each mother, ranging from 0.23% to 0.52% per liter of milk, but then declined at a rapid rate, reaching a plateau after 24 hours. The researchers concluded that if an infant were to nurse from a mother taking 30 mg of prednisolone a day, the amount that would be transferred through the milk would be minuscule.[22]

In the remaining three studies, prednisolone was administered through an intravenous injection rather than via the oral route.[23-25] In one study, three women were given 50 mg prednisolone phosphate through an IV line over 10 seconds.[24] For 6 hours post-injection, the

women used a breast pump to retrieve milk from alternate breasts every hour until empty, after which the samples were analyzed. An average of 0.025% of the administered prednisolone was recovered in the milk.[24] This percentage is very low when compared to the 10% cut off that is considered safe for breastfeeding, which is stated by the authors.

The second study followed a 36-year old female who received a standard dose of 1000 mg IV methylprednisolone sodium succinate over 2 hours on 3 consecutive days.[23] She collected her breast milk at 0, 1, 2, 4, 8, and 12 hours after the dosage each day. The samples were then analyzed for drug concentration. The relative infant dosage was calculated to be 1.45%, 1.35%, and 1.15% for days 1, 2, and 3, respectively. Compared to the theoretical level of concern for medications in breast milk (>10%), these levels are relatively low.[23]

A very similar study was conducted on a 39-year old patient with MS.[25] She received a dose of 1000 mg/day of methylprednisolone and milk samples, taken at 4 hours and 8 hours post-dosage, were screened through chromatography. Researchers found that when comparing methylprednisolone levels at 4 hours and 8 hours after the injection, drug concentration was significantly decreased at the 8 hour mark from 3.0 mg/L to 0.048 mg/L. Therefore, they concluded that it is safe to breastfeed while on this drug but recommend that a mother wait 8 hours after taking methylprednisolone to breastfeed her infant.[25] This, however, would mean that the mother would have to carefully plan pumping her milk around her treatment. For the typical treatment regime that lasts over three to five days, this could be difficult to do, especially if the mother has frequent acute exacerbations.

Since the literature identified consisted only of case reports/case series, the strength of evidence for this medication is weak and completion of one or more RCTs would help to increase understanding of risk to breastfed infants. However, medications that are given through

IV are likely to be higher in breast milk, as opposed to those taken orally. Since two studies showed that the infant dosage delivered by a mother receiving an IV dose of methylprednisolone is relatively low, the oral form of prednisolone is even less likely to cause adverse effects in infants.[23,24] This means that if a mother did not want to receive IV therapy, oral prednisolone is a viable alternative for treating relapses and is likely to be safe for use during breastfeeding.[49] However, prescribing information for methylprednisolone does not provide any information on milk transfer in humans or any animals, and women should always consult with their healthcare provider to plan an appropriate course of action.[50]

Intravenous immunoglobulin

Intravenous immunoglobulin is an antibody that has several different mechanisms used to modulate the immune system.[51] It can inhibit the binding of pathological antibodies and may be able to assist with remyelination.[51] The dose of intravenous immunoglobulin also depends on the severity of the condition, but can be administered every 3-4 weeks.[52]

There were no studies identified that specifically looked at immunoglobulin levels in breast milk. However, in a retrospective evaluation, three groups of pregnant women with *relapsing-remitting* MS were studied for relapse rate and the effect of the drug during pregnancy and the postpartum period.[26] The first group consisted of women who received a dose of 0.4 g/kg body weight/day for 5 consecutive days within the first week after delivery, and additional booster doses of 0.4 g/kg body weight/day at 6 and 12 weeks postpartum. The second group was treated continuously with IV Ig during the gestation and postpartum periods (0.4 g/kg body weight/day). This included a period of 5 consecutive days within the 6-8 weeks of gestation then additional booster doses of 0.4 g/kg body weight/day were administered once every 6 weeks until 12 week postpartum. The final group received no treatment. Assessment of breastfeeding

behavior was not an objective of this study. However, the authors reported that about 73% of the infants were breastfed for at least 3 to 12 weeks and that no adverse effects were observed in these infants.[26]

Research done specifically on immunoglobulin levels in breast milk would provide better evidence for safety of use during breastfeeding. This strongest evidence would be provided by a RCT.[28] Prescribing information provides no information on transfer into human or animal milk and does not provide a statement on use during breastfeeding.[53] Therefore, mothers should consider this gap in research when planning to breastfeed.

DISCUSSION

This systematic review of original research investigating the use of MS medications during lactation identified a significant gap in the literature. What research has been completed indicates that, of the ten drugs identified as being used for treatment of MS, only four were found to be safe to use during lactation: *interferon β, glatiramer acetate, prednisolone,* and *immunoglobulin*.[18-20,22-25] Despite their likely safety, both *interferon β* and *glatiramer acetate* are still only given a lactation risk category of L3 by Dr. Thomas Hale, the executive director of the Infant Risk Center, meaning they are considered to be moderately safe to use in this situation.[54,55] *Prednisolone* and *immunoglobulin* have a lactation risk category of L2, which means they are considered safer to use during breastfeeding than medications in the L3 category but have only been studied in a limited number of breastfeeding women.[55] Since *natalizumab, mitoxantrone, alemtuzumab, fingolimod,* and *teriflunomide* are all shown to be excreted in milk, they are considered possibly hazardous and/or are contraindicated during lactation, even though there is no evidence of adverse effects in infants.[55] Since it is unknown whether dimethyl fumarate is

excreted in either human or animal milk, there is no lactation risk category assigned. However, even with the abundance of drugs that are contraindicated during lactation, it is not recommended that mothers avoid breastfeeding altogether.[56] Most mothers with MS are encouraged to breastfeed if they are able to withstand discontinuing their drug therapy for the duration of their lactation experience.[56]

Limitations

The research completed on the transfer of drugs into breast milk is very limited. Overall, there is a paucity of published reports that confirm risk of adverse effects to infants.[57] While there are some studies that imply safety of use for certain medications, randomized control trials would provide much stronger evidence for these claims. However, randomized control trials generally cannot be conducted due to the ethical issue of randomizing a mother to breastfeed or formula feed. The drug component of the studies causes more issues, as the type of drug, dosage, and frequency of dosage would be dependent on the type and severity of the mother's MS. Administering a standard dose could be detrimental to the mother's health if she requires more than this amount. Also, since it has been found that *natalizumab, mitoxantrone, alemtuzumab, fingolimod,* and *teriflunomide* are excreted in milk, it is unethical to allow infants to receive breast milk from mothers taking these drugs, as it is unknown how this might impact infant health and well-being. The studies that have been conducted also have very small sample sizes, which makes it more difficult to generalize to other populations. Due to these ethical barriers, most instructions on safe drug use during lactation are based on case reports or single case studies that measure breast milk or infant serum drug levels, resulting in decisions made based on weak study designs[57]

One limitation of this systematic review is that articles not available in English were not included. Both time constraints and lack of access to translation services prevented use of these articles. Another limitation, for systematic reviews in general, is that studies that have more impressive results are more likely to be published and subsequently identified by other researchers, meaning there is some element of publication bias present.[58] Finally, relevant information might have been excluded, secondary to the choice of key words.

Context

Other literature reviews on maternal to infant drug transfer have often focused on medication use during pregnancy (maternal-fetal transfer), due to the abundance of research in this area. While breastfeeding information is usually included in these articles, this review is unique in that the goal was to focus solely on breastfeeding. In doing so, it has highlighted the lack of research that has been completed on this topic within the search time span of 1950-2016. The studies identified by this systematic search were the same studies included in other systematic reviews completed on this topic. The lack of new literature indicates a need for more studies to be conducted, specifically for *mitoxantrone, alemtuzumab, fingolimod, teriflunomide,* and *dimethyl fumarate*, information for which all came from prescribing information, likely due to the absence of any other available sources.

Future Direction

Research has shown that most medication given to a mother will pass to a breastfeeding infant, with the exception of those with large molecular weight.[59] This means that the real concern is not if a medication is excreted, but how much of it is excreted and if that amount poses a risk to the infant. In order to establish the risk of a drug to a neonate, it is important to be able to predict the amount of the drug presented to the infant following administration via milk.[59]

More detailed research studies, specifically on the drugs *mitoxantrone, alemtuzumab, fingolimod, teriflunomide,* and *dimethyl fumarate,* need to be organized in order to determine fully if these drugs should remain contraindicated for use during breastfeeding. While these drugs are excreted in milk, that alone does not provide a definitive reason to avoid breastfeeding.

Report of adverse effects in literature does not necessarily define an absolute contraindication, but does implore the use of caution when using drugs, by monitoring the infant for both physical and behavioral changes.[57] Breastfeeding has been shown to be beneficial for infants for both cognitive and immune system development.[9] If mothers with MS are able to breastfeed without giving up medication they need, infants will be better able to gain the full advantages of breast milk without forfeiting the well-being of the mother. However, until these drugs can be explored further, mothers should evaluate the benefits of breastfeeding against the benefits of their drug therapy and consult their doctor about determining whether they should breastfeed, continue their medication, or switch to another disease-modifying drug which is safer to use while breastfeeding.

CONCLUSION

Only four medications used in the treatment of MS are considered safe to use while breastfeeding. *Interferon-β, glatiramer acetate,* and *prednisolone* are not secreted in human milk at significant levels and no adverse effects in infants have been found. While it is not known whether *intravenous immunoglobulin* is secreted in breast milk, it has not been shown to cause detrimental side effects in infants. *Natalizumab* and *mitoxantrone* are excreted in human milk, but it is unknown whether they cause any harm. *Fingolimod* and *teriflunomide* have been found to be excreted in rodent milk while *alemtuzumab* has been found to be excreted in murine milk.

It is unknown whether dimethyl fumarate is excreted in the milk of either of these species. *Natalizumab, mitoxantrone, fingolimod, teriflunomide, alemtuzumab,* and *dimethyl fumarate* are not recommended to use while breastfeeding. However, this recommendation appears to be due more to lack of research and considerable precaution with infant health than with results of carefully planned and implemented studies.

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