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Breastfeeding and treatment for multiple sclerosis

PERSPECTIVES

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Monoclonal antibody therapy is effective for multiple sclerosis, and only small amounts of antibodies are transferred to breast milk. Even though the approved product descriptions advise against breastfeeding during medicinal treatment, several of the most effective MS drugs are compatible with breastfeeding.

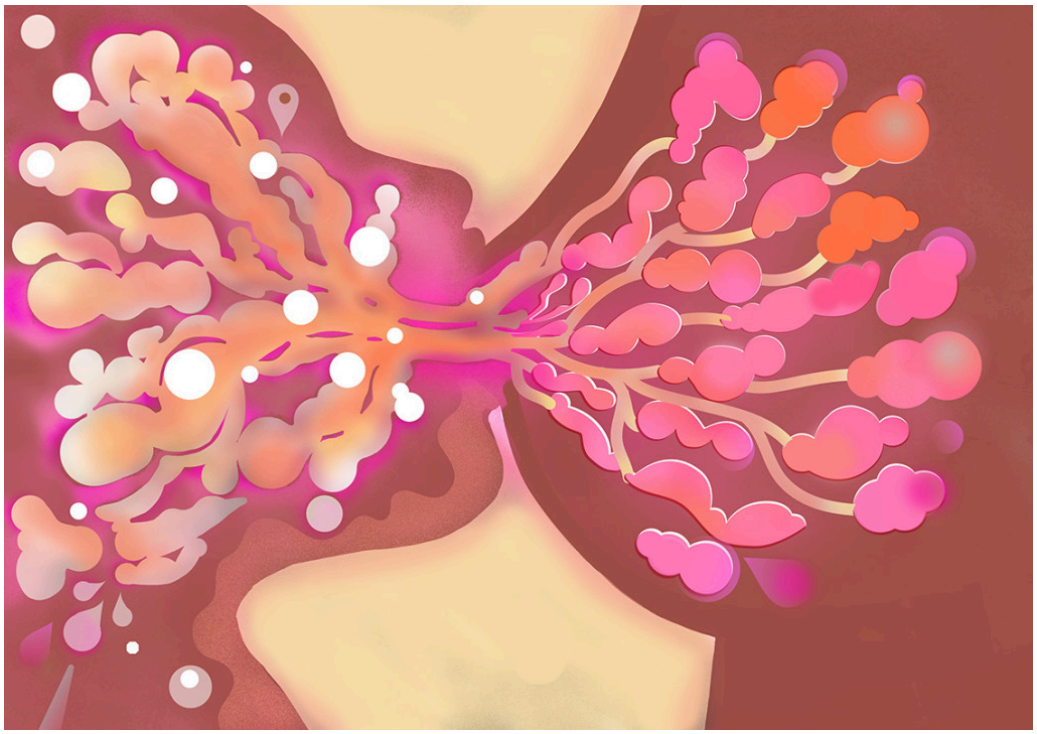

Illustration: Isabel Albertos

In 2016, we published a review article on the treatment of multiple sclerosis (MS) for pregnant and nursing women (1). Breastfeeding has numerous health benefits for mother and child and is associated with a lower risk of postpartum relapses in women with MS (2). The postpartum period is also a high-risk time for MS relapses (3). It is therefore important to initiate treatment quickly.

Product descriptions in the Norwegian Pharmaceutical Product Compendium advise against breastfeeding when taking the most commonly used MS drugs, including monoclonal antibodies. This has created a dilemma, where patients have had to choose between either not breastfeeding and starting treatment or breastfeeding and postponing treatment, leading to an increased risk of debilitating MS relapses. In studies into the transfer of drugs into breast milk, the infant's relative dose intensity is typically specified, which is the proportion of the dose that the infant receives via the breast milk relative to the mother's dose, adjusted for the mother's and child's body weight. A relative dose intensity of less than 2 % is considered minimal, and relative doses of up to 10 % are normally acceptable (4). However, when assessing whether breastfeeding is safe, the toxicity of the drug must also be considered. In a few medications, such as cytostatics, even a minimal infant dose is not acceptable (4).

> ***«Patients have had to choose between either not breastfeeding and starting treatment or breastfeeding and postponing treatment»***

In recent years, new drugs and new knowledge about breastfeeding and the use of biological medicines have emerged. Here we provide an update and give our recommendation for treatment in nursing mothers with MS.

Injectable medications

Glatiramer acetate and interferon-β are large molecules that are denatured in the gastrointestinal tract. They have therefore traditionally been regarded as the safest MS medications for nursing mothers (1). New safety and follow-up data on children confirm that breastfeeding is safe during treatment with these medications (5).

Low molecular weight drugs in tablet form

Sphingosine-1-phosphate receptor modulators (fingolimod, siponimod, ozanimod) and teriflunomide are likely to pass into breast milk and can be absorbed from the infant's gastrointestinal tract. We still advise against use by nursing mothers. For dimethyl fumarate, recent data from two patients showed very low concentrations of the active metabolite in breast milk, corresponding to 0.019 % and 0.007 % of the maternal dose respectively (6). This suggests that breastfeeding is probably safe, but there is still insufficient data to recommend this. Cladribine has a long-lasting pharmacodynamic effect on the immune system, and the treatment can usually be staggered and thus adapted to the breastfeeding. The medication has a short half-life, and data from a single case study only showed measurable concentrations in breast milk shortly after treatment ended (7). As cladribine is lipophilic and exposure can have potentially harmful effects for the breastfed infant, we recommend, in line with the product description, no breastfeeding for the first seven days after treatment has stopped.

Monoclonal antibodies

Rituximab

Rituximab is a cytotoxic antibody that kills circulating B cells. Because of its high efficacy and low price, rituximab is frequently used to treat MS. A cohort study shows that the rituximab concentration in breast milk is very low, and the dose the infant is exposed to via breast milk is only around 0.08 % of the maternal dose (8). We have recently published a patient series of six women with relapsing-remitting MS (9) who had similar rituximab concentrations in breast milk, and there were no measurable levels of infant serum rituximab concentrations (< 0.01 µg/mL). The level of B cells was normal in all the children. This suggests minimal transfer to breast milk and no absorption of rituximab by the breastfed infant.

Ocrelizumab and ofatumumab

Both ocrelizumab and ofatumumab are humanised antibodies that, like rituximab, kill B cells. They are likely to have the same low transfer to breast milk and serum in the breastfed infant as rituximab. However, there is no published data on use of these medications in nursing mothers.

Natalizumab

A recently published article showed that the concentration of natalizumab in breast milk in eight patients was low and that the dose the infants were exposed to via breast milk was 0.04 % of the maternal dose (10). No data are available on the level in the serum of the breastfed infant, but it is likely that natalizumab is broken down in the infant's gastrointestinal tract and is not absorbed, in the same way as for rituximab.

Alemtuzumab

There are no published data on the use of alemtuzumab in nursing mothers. Based on existing knowledge about other monoclonal antibodies, the transmission to breast milk is probably small. As the medication has a long-lasting effect on the immune system, treatment during breastfeeding is rarely necessary.

Treating relapses

MS relapses are typically treated with high-dose steroids. We have previously advised against steroid treatment for nursing mothers (1). However, recent studies have shown that the transmission to breast milk is low, and the infant is only exposed to 0.50 % of the maternal dose (11). We therefore believe that the evidence now indicates that it is also safe to treat relapses with steroids during the breastfeeding period. To further reduce the concentration, the mother can wait 2–4 hours to breastfeed after ingestion.

Our recommendations

In recent years, significant advancements have been made in our knowledge of breastfeeding and the medicinal treatment of nursing mothers with MS, particularly for monoclonal antibodies. We know there is little transfer of monoclonal antibodies to breast milk due to their high molecular weight (around 145 000 daltons), and most of it is denatured in the infant's gastrointestinal tract. Furthermore, there is little or no absorption of antibodies through the infant's mucosa (12). As a general rule, we believe there is sufficient evidence to recommend that breastfeeding is safe in women receiving monoclonal antibody therapy. Paradoxically, the evidence on use in nursing mothers is better for rituximab – which is used to treat multiple sclerosis off

label – than for the medications with marketing authorisation. The older medications glatiramer acetate and interferons are also safe, but are far less potent.

> ***«As a general rule, we believe there is sufficient evidence to recommend that breastfeeding is safe in women receiving monoclonal antibody therapy»***

Colostrum, which is produced in the first few days after childbirth, has a different composition from mature breast milk (9). As the data for breastfeeding mostly relate to more than 14 days after childbirth, we recommend that most nursing mothers wait until after this period to start MS treatment. Premature infants can have higher absorption and poorer excretion of medication than other infants, which may indicate that some should wait more than 14 days.

The duration of treatment effect varies considerably between different MS drugs. Cladribine, alemtuzumab and, to some extent, rituximab and ocrelizumab have a long-lasting pharmacodynamic effect. For these medications, it is relatively easy to adapt breastfeeding to the treatment regime.

Natalizumab and sphingosine-1-phosphate receptor modulators have a more short-lived effect and are associated with symptom flare-ups after treatment is discontinued. Women who discontinued these medications before or during pregnancy are particularly at risk of severe relapses during the postpartum period (13). We therefore recommend that women treated with a sphingosine-1-phosphate receptor modulator before pregnancy change to a monoclonal antibody if they want to breastfeed.

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