BREASTFEEDING MEDICINE
Volume 15, Number 2, 2020

DOI: 10.1089/bfm.2019.0280

Breastfeeding After Organ Transplantation

Philip O. Anderson

Organ transplantation can allow women with failing organs to become pregnant and deliver healthy infants. A registry of post-transplant women who became pregnant and breastfed is maintained by the Transplant Pregnancy Registry International (formerly the National Transplantation Pregnancy Registry).[1] The Registry reported that the rate of breastfeeding after transplantation overall rose from <10% in the early 1990's to 35% in 2012 and was as high as 44% with kidney transplantation in 2010.[2,3] The improving breastfeeding rate reflects the increased experience with antirejection drugs, and evidence for their safety during breastfeeding. The Registry has collected outcome data on 424 infants who were breastfed by transplanted mothers.

Depending on the organ that was transplanted, various combinations and target concentrations of immunosuppressants are used. The most commonly used drugs are reviewed in this column. Additional literature references on specific drugs can be found in the corresponding LactMed® records.

Tacrolimus

Tacrolimus is a calcineurin inhibitor that is the first-line antirejection therapy for most transplants. Amounts of systemically administered tacrolimus are low in breast milk and probably do not adversely affect the breastfed infant. Among 32 breastfed infants whose mothers were taking tacrolimus, most had undetectable serum concentrations. At 14 days of age, breastfed infants who did have detectable concentrations at birth from transplacental transmission had blood concentrations that were no higher than infants who did not breastfeed. This indicates infants eliminate tacrolimus and that breastfeeding does not add to existing serum levels. Investigators from the United States, clinicians from the Transplantation Pregnancy Registry, and other experts consider tacrolimus acceptable to use during breastfeeding after organ transplantation.

Cyclosporine

Cyclosporine is the oldest antirejection drug in the calcineurin inhibitor class, but it is no longer a first-line drug. Milk cyclosporine concentrations are variable, and it has poor and erratic absorption, which minimizes the dose the infant absorbs. With typical maternal cyclosporine blood concentrations, a completely breastfed infant usually receives no more than about 2%, and often <1%, of the mother's weight-adjusted dosage or pediatric transplantation maintenance dosage. Most infants studied have not had detectable cyclosporine blood concentrations, but two reported infants had measurable concentrations, one with blood concentrations in the therapeutic range despite relatively low maternal milk concentrations.

Numerous infants have been breastfed during maternal cyclosporine use, usually with a concurrent corticosteroid and sometimes with concurrent azathioprine. No reports of adverse effects on infant growth, development, or kidney function have been reported. At least two transplanted mothers successfully breastfed a second infant after successfully breastfeeding their first infant. The Transplantation Pregnancy Registry and other experts consider cyclosporine to be safe to use during breastfeeding. Breastfed infants should be monitored if this drug is used during lactation, possibly including measurement of serum concentrations to rule out toxicity if there is a concern.

Mycophenolate Mofetil

Mycophenolate mofetil is often used in combination with a calcineurin inhibitor. It is contraindicated during pregnancy. Some pregnant women who cannot be on calcineurin inhibitor monotherapy are given azathioprine in place of mycophenolate. Consequently, only few infants have been breastfed during mycophenolate therapy and no information is available on its excretion into breast milk. The Transplantation Pregnancy Registry has collected information on six mothers (five kidney and two heart transplants) who breastfed seven infants while taking a mycophenolate product. The maximum time that any of the infants breastfed was 14 months. None of the infants had any reported adverse reactions. However, because so little information is available on the use of mycophenolate during breastfeeding, most sources recommend avoiding it in nursing mothers.[3]

Azathioprine

Azathioprine has been largely replaced by mycophenolate mofetil because of its better tolerability and efficacy. Although now relegated to second-line therapy, azathioprine was used commonly in the early transplant era, so considerable evidence is available. Most experts consider breastfeeding during azathioprine therapy to be acceptable. Doses

Division of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California.

of up to 200 mg/day for immunosuppression result in either low or unmeasurable concentrations of the active metabolites in milk and infant serum. Avoiding breastfeeding for 4 hours after a dose should markedly decrease the dose received by the infant in breast milk. A case–control study of 14 infants followed for up to 6 years of age found no difference in the number of hospitalizations or the rate of infections compared with a control group. Mild asymptomatic neutropenia has been reported, although infrequently, and the value of routine monitoring is debatable.

Sirolimus and Temsirolimus

Sirolimus is a structural analogue of tacrolimus, but it inhibits the second phase of T cell activation, rather than the first phase such as tacrolimus and cyclosporine. Only one infant has been reported who was breastfed during maternal therapy with sirolimus plus tacrolimus and prednisone in unspecified dosages after a kidney–pancreas transplant. The authors who followed the mother knew of no serious side effects in the infant.

Temsirolimus is an ester prodrug of sirolimus that is given intravenously (IV). It is metabolized to sirolimus as well as other metabolites. Because almost no information is available, breastfeeding is considered to be inadvisable with these two drugs. The manufacturer recommends not breastfeeding during temsirolimus therapy and for 3 weeks after the last dose.

Everolimus

Everolimus is an analogue of sirolimus with a similar mechanism of action. Only two patients have been reported who took everolimus during pregnancy and had colostrum concentrations measured. In one patient, everolimus was not detected in milk while taking 2 mg/day. In the other mother who took a lower dose of 0.5 mg/day, the milk concentration increased from 33 μg/L before the dose to 66 μg/L after the dose. Serial serum samples in the infant estimated an elimination half-life of about 86 hours for everolimus obtained transplacentally. No infants were reported to have been breastfed during maternal everolimus use, so breastfeeding should be avoided until more data become available. The manufacturer recommends avoiding breastfeeding for 2 weeks after the last dose.

Belatacept

Belatacept is a soluble fusion protein that is a selective T lymphocyte costimulation blocker. Belatacept is used in combination with basiliximab induction, mycophenolate mofetil, and a corticosteroid. It is only indicated for use in Epstein-Barr virus seropositive patients. No information is available on its use during breastfeeding or its excretion into breast milk. Because the drug's half-life is 8–10 days, it may be more than a month after a dose before the drug is absent from breast milk. In general, breastfeeding is discouraged during belatacept therapy, especially since it must be used with other drugs that have little breastfeeding information.[3]

Corticosteroids

A low-dose corticosteroid, usually prednisone, is used for transplant maintenance therapy. High-dose boluses, usually of IV methylprednisolone, are used for disease flares. These drugs do not enter milk well. Older advice was to withhold breastfeeding for a period of time after a dose. This is no longer thought to be necessary with maintenance doses. Even methylprednisolone IV bolus doses of up to 1 g do not pose a risk to the breastfed infant, but withholding breastfeeding for 2–4 hours after a dose will markedly reduce the dose of methylprednisolone that an infant receives.

Antibodies

Some antibodies are used to treat acute rejection and graft versus host disease. Because antibodies are large protein molecules with high molecular weights, the amounts in milk are likely to be very low and absorption is unlikely because the antibodies are probably destroyed in the infant's gastrointestinal tract. Antithymocyte globulin is a polyclonal antibody from either horse or rabbit serum and used for acute organ rejection after transplantation. No information is available on its excretion into breast milk in humans, nor on its use during breastfeeding. Basiliximab is a monoclonal antibody that is an interleukin-2 receptor antagonist. It is indicated for prophylaxis of acute organ rejection in patients receiving renal transplantation.

Because no information is available on the clinical use of either of these drugs during breastfeeding, the manufacturers recommend that breastfeeding be discontinued during therapy. Several other monoclonal antibodies and globulins are considered acceptable to use during breastfeeding, so if data eventually become available, these drugs might also be acceptable.

Rituximab is a murine/human monoclonal antibody that targets CD20, a B cell-specific surface antigen. It is used in transplant patients for the treatment of graft-versus-host disease. After doses of 0.5–1 g milk levels are very low, in the range of 0.06 to 0.12 mcg/mL. This corresponds to a relative infant dosage of 0.1% or less. Even one outlier patient who had an unusually high milk level would have only transmitted $\sim$0.3% of the maternal dosage to her infant.[4]

Several infants have been breastfed safely with maternal rituximab use, with follow-up between 8 and 12 months in four of the infants. It appears that risks to breastfed infants are low.

Summary

The most commonly used antirejection drugs used after organ transplantation, cyclosporine, tacrolimus, corticosteroids, azathioprine and probably rituximab, are acceptable during breastfeeding. However, they should be used with caution while nursing a newborn or preterm infant. Some transplant drugs should be avoided currently because of a lack of information rather than known risk to the infant. These are mycophenolate, everolimus, sirolimus, temsirolimus, antithymocye globulin, and basiliximab. As more information becomes available, they also might be considered acceptable to use. Belatacept will probably remain as a contraindication to breastfeeding for the foreseeable future.

Acknowledgment

The author thanks Linda Awdishu, PharmD, MAS, for her review of the article and comments.

Disclosure Statement

No competing financial interests exist.

References

1. Transplant Pregnancy Registry International. 2017 Annual Report. Transplant Pregnancy Registry International (TPR) Gift of Life Institute Philadelphia, PA, 2018.
2. Armenti VT, Moritz MJ, Davison JM. Breastfeeding and tacrolimus: Is it a reasonable approach? *Expert Rev Clin Immunol* 2013;9:623–626.
3. Constantinescu S, Pai A, Coscia LA, et al. Breast-feeding after transplantation. *Best Pract Res Clin Obstet Gynaecol* 2014;28:1163–1173.
4. Krysko KM, LaHue SC, Anderson A, et al. Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurologic conditions. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e637.

Address correspondence to:
Philip O. Anderson, PharmD
Division of Clinical Pharmacy
Skaggs School of Pharmacy
and Pharmaceutical Sciences
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0657

E-mail: phanderson@ucsd.edu