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Antivirals for COVID-19 and Breastfeeding

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Many drugs are being investigated for treatment of COVID-19. The *Medical Letter on Drugs and Therapeutics* maintains an excellent, periodically updated and well-referenced table of anti-COVID-19 drugs that is free to download.[1] Additional information about ongoing trials can be found at clinicaltrials.gov. This column will review the use in breastfeeding of the most prominent drugs that might be active against the SARS-CoV-2 virus that causes the disease. Additional breastfeeding references on specific drugs can be found in the corresponding LactMed records.

Remdesivir

Remdesivir inhibits viral RNA replication by blocking RNA-dependent RNA polymerase. It is moderately effective in reducing symptoms and hastening recovery in hospitalized patients with severe infections. U.S. National Institutes of Health (NIH) guidelines recommend a duration of 5 days for hospitalized patients with severe COVID-19 who are not intubated; duration may be extended up to 10 days for mechanically ventilated patients, those on extracorporeal membrane oxygenation, or in those who have not improved after 5 days of treatment. Mothers with disease this serious probably would not breastfeed their infants, but clinical studies on patients with less severe infections are underway. Remdesivir is given by intravenous (IV) infusion because it is poorly absorbed orally, so infants are not likely to absorb clinically important amounts of the drug from milk. In addition, newborn infants have received IV remdesivir therapy for Ebola with no serious adverse drug reactions. Given this limited information, it does not appear that mothers receiving remdesivir need to avoid nursing, but until more data are available, remdesivir should be used with careful infant monitoring during breastfeeding. The most common adverse effects reported after IV infusion include elevated aminotransferase and bilirubin levels and other liver enzyme elevations, diarrhea, rash, renal impairment, and hypotension.

Favipiravir

Favipiravir is a viral RNA polymerase inhibitor approved for influenza overseas that is being tested for use against COVID-19. It is not approved by the U.S. Food and Drug Administration (FDA), but a few studies are open for enrollment in the United States for COVID-19 treatment. Some preliminary results in COVID-19 from outside the United States appear promising, but high-quality studies have not been reported. In clinical trials, favipiravir has been well tolerated, but has caused liver enzyme abnormalities, gastrointestinal symptoms, and serum uric acid elevations. One unique feature of favipiravir is that it is contraindicated for use in pregnant women because of animal teratology studies. Men taking the drug are recommended to avoid intercourse with pregnant women during treatment and for at least 7 days after the last dose.

No information is available on the use of favipiravir during breastfeeding or its excretion into breast milk. Favipiravir is a small molecule that is about 60% protein bound in plasma, so it would be expected to appear in breast milk and be absorbed by the infant, probably in small amounts. If favipiravir is used in a nursing mother, typical adverse reactions should be monitored in the breastfed infant.

HIV Protease Inhibitors

Several HIV protease inhibitors are being studied for treating COVID-19. NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data. Among the most mentioned agents are atazanavir, darunavir plus cobicistat, and lopinavir plus ritonavir. Breastfeeding information is varied with these drugs. No published information is available on the use of darunavir with or without cobicistat during breastfeeding. Amounts of atazanavir in milk appear to be low based on data from three women. Lopinavir has been the best studied. It appears in breast milk in low levels but has been found in the serum of some breastfed infants. No adverse infant effects have been clearly caused by lopinavir in breast milk.

Interferons

Interferon beta-1b and ribavirin is a combination previously used to treat chronic hepatitis C infection that is now being studied in COVID-19. Interferon beta-1a is also being studied in combination with remdesivir in hospitalized patients. Interferon beta-1b has not been studied in breast milk, but levels of interferon beta-1a in breast milk are minuscule. In addition, because interferon is poorly absorbed orally, it is not likely to reach the bloodstream of the infant. Many women have breastfed while taking interferon beta-1a with no adverse infant effects reported. Expert consensus considers beta interferons to be acceptable during breastfeeding. Ribavirin has not been studied in nursing mothers, but ribavirin

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is given directly to infants by inhalation to treat respiratory syncytial virus (RSV) infection. The amount in milk is likely to be lower than the doses received by infants treated with ribavirin for RSV infection.

Antibody Therapy

Several forms of antibody therapy exist or are being developed. Passive antibody therapy by infusion of convalescent plasma obtained from patients who have recovered from COVID-19 may prevent infection or reduce severity of illness. It has improved patient outcomes in uncontrolled case series and trials, primarily in severely ill hospitalized patients. It is most likely to be effective when given as prophylaxis or early in the disease.

At the beginning of the pandemic, Chinese physicians used IV immune globulin (IVIG) to treat severely ill patients. Since the immune globulin was taken from patients with no known exposure to SARS-CoV-2, it is unlikely that specific antibodies were present. A retrospective study of 58 patients in Wuhan found that administration of IVIG within 48 hours of hospital admission was associated with reduced 28-day mortality, a shorter hospitalization, and reduced ventilator use compared with administration after 48 hours. Immune globulin is a normal component of breast milk. IgG concentrations in milk are normal or higher and IgM levels in milk are normal or lower during IVIG therapy. The antibacterial activity of milk in these women was normal. Neither convalescent plasma nor IVIG appear to be a risk for the breastfed infant.

Work is also being done to develop monoclonal antibodies against SARS-CoV-2 as single or combinations of highly active antibodies. Should these become available, concerns with breastfeeding are minimal. Monoclonal antibodies have very low levels in breast milk because of their high molecular weight and they are poorly bioavailable in breastfed infants because they are likely destroyed in the infant's gastrointestinal tract, at least after the first few days postpartum. Only monoclonal antibodies used to treat cancer are currently considered to be problematic during breastfeeding. Monoclonal antibodies against SARS-CoV-2 would be unlikely to be a danger for the breastfed infant.

Famotidine

Computer simulation suggests that famotidine may inhibit the 3-chymotrypsin-like protease required for replication of SARS-CoV-2. A case series and two retrospective chart review studies found that famotidine decreased the risk of intubation and death by about 60% in hospitalized patients. Prospective studies are underway. After doses of 40 mg, famotidine appears in milk in low levels that are not of concern. Although doses being used in some studies for COVID-19 have been >40 mg/day, famotidine is a safe drug that is given directly to newborn infants in higher dosages than are transmitted in breast milk, so it would not be expected to cause any adverse effects in breastfed infants.

Antimalarials

The antimalarials chloroquine and hydroxychloroquine have been prominent in the news, but these drugs have not performed well against COVID-19 in controlled clinical trials. The FDA issued a Drug Safety Communication warning against use of these drugs outside of a clinical trial because of the risk of serious cardiac arrhythmias, including QT prolongation, and they are not recommended for treatment of outpatients. Hydroxychloroquine has had to be stopped early in some patients in clinical trials because of adverse effects. Very small amounts of chloroquine and hydroxychloroquine are excreted in breast milk; however, hydroxychloroquine data in breastfeeding are much more robust. In infants up to at least 1 year of age, careful follow-up found no adverse effects on growth, vision, or hearing. International expert opinion finds hydroxychloroquine acceptable during breastfeeding.

Azithromycin

Azithromycin has been used alone and with hydroxychloroquine. Most trials have been of modest quality (e.g., retrospective, open label) and efficacy has not been impressive. The combination with hydroxychloroquine may cause QT interval prolongation and liver enzyme elevations. NIH recommends against the use of this combination, except in clinical trials because of its toxic potential. Because of the low levels of azithromycin in breast milk and use in infants in higher doses than appear in milk, it is not expected to cause adverse effects in breastfed infants. Monitor infants for possible effects on the gastrointestinal flora, such as vomiting, diarrhea, candidiasis (i.e., thrush, diaper rash). Unconfirmed epidemiological evidence indicates that the risk of infantile hypertrophic pyloric stenosis might be increased by maternal use of macrolide antibiotics, but this relationship is questionable.

Ivermectin

Ivermectin inhibits SARS-CoV-2 in vitro, possibly by inhibiting nuclear transport activity. An uncontrolled, retrospective study found a decreased risk of mortality in patients taking ivermectin. Data from four nursing mothers indicate that ivermectin is poorly excreted into breast milk after oral administration. Amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants.

Nitazoxanide

In attempts to find prospective antivirals against SARS-CoV-2, researchers have combined data from in vitro testing of anti-infective drugs against SARS-CoV-2 with the drug pharmacokinetic data to identify prospective candidates that could be repurposed to treat COVID-19. A drug that has been identified this way by two different groups is nitazoxanide. Numerous studies are registered at ClinicalTrials.gov for nitazoxanide alone or in combination with other drugs, but results are not yet available. After oral administration, nitazoxanide is not found in the bloodstream, but is rapidly converted to the active metabolites, tizoxanide, and tizoxanide glucuronide, which are detectable in maternal plasma. Information from one mother indicates that a dose of 500 mg of nitazoxanide produces low levels of tizoxanide in breast milk. COVID-19 study doses are about 1–2 g/day.

Vitamin D

Limited data from observational nonpeer-reviewed studies suggest that vitamin D levels might decrease the severity of COVID-19 in persons with vitamin D deficiency. There is no evidence that high-dose vitamin D would treat the disease or that persons with adequate vitamin D levels would be helped by it. Vitamin D is a normal component of human milk. Daily maternal vitamin D supplementation in the 400–2,000 IU (10–50 mcg) range produces milk concentrations that are inadequate to deliver the daily requirement to an exclusively breastfed infant, and inadequate to correct pre-existing infant vitamin D deficiency through breastfeeding alone. Daily maternal vitamin D dosages at or >4,000 IU (100 mcg) achieve milk levels can potentially meet the daily infant goal intake of at least 400 IU, depending on the mother's underlying vitamin D status and daily infant milk intake.

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Reference

1. Treatments considered for COVID-19. *Med Lett Drugs Ther* 2020. Available at https://secure.medicalletter.org/downloads/1595e_table.pdf (accessed September 2, 2020).

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