

# Lactation and the Use of Biologic Immunosuppressive Medications

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## Abstract

Biologic medications are effective therapeutic options for treating autoimmune diseases, but information on their safety in lactation is still scarce. Autoimmune conditions occur frequently in women of childbearing age, creating difficult decisions regarding optimizing maternal health and supporting breastfeeding. Available data, in addition to the favorable pharmacokinetic properties of biologics, suggest that these medications are compatible with breastfeeding. A review of the available evidence and information is presented, as well as recommendations on counseling the nursing mother and her healthcare team to make informed decisions about maternal and infant care.

## Introduction

**A**UTOIMMUNE DISORDERS ARE CHRONIC health conditions caused by the immune system attacking the body's healthy cells. They are particularly common in women of childbearing age and can greatly impact quality of life.<sup>1</sup> Biologic medications are a relatively recent therapeutic option and are used instead of or in addition to oral therapies. This article will focus on the common biologic treatments indicated for various autoimmune conditions (such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis) in regard to their use in lactating mothers. A PubMed search was performed with the term "breastfeeding" and a combination of the names of specific medications, as well as "lactation" combined with medication names. The search was limited to English language and human subjects. In addition, the LactMed database was searched, and relevant print references were consulted.

## Introduction to Biologics

Medications known as "biologics" or "biopharmaceuticals" are large protein molecules synthesized in living cells.<sup>2</sup> They are parenterally administered because of poor absorption in the gastrointestinal tract. Recent guidelines for relevant autoimmune conditions include the use of biologic agents, either as monotherapy or with other medications such as methotrexate.<sup>3,4</sup> They are usually reserved for patients with moderate to severe disease and those who cannot use oral agents.<sup>3-5</sup>

## Use in Lactation

Because biologics are a newer therapeutic option, there is limited information regarding their use in lactation. There are

published reports available for some medications, which indicate no noted adverse effects in the breastfed infants or detrimental effect on lactation. In the case of the medications that lack any human lactation data, their pharmacokinetic properties must be assessed in order to estimate their safety. Because biologics have high molecular weights, they likely transfer into breastmilk only in small amounts, if at all.<sup>6</sup> However, during the first 3 days postpartum the breast alveolar cells have wide gaps between them, allowing larger molecules such as immunoglobulins to pass through into the milk.<sup>6</sup> Thus, the timing of the first postpartum dose of a biologic medication should be considered, as it may impact the extent of transfer into breastmilk. Because biologics are protein molecules, they would likely be destroyed by the acids and proteolytic enzymes in the infant's gastrointestinal tract and therefore not be absorbed.<sup>6,7</sup> Despite the apparent low level of risk of using biologics during lactation, recommendations from industry and medical experts can be conflicting. Pharmaceutical manufacturers generally state that women should not breastfeed while using these medications.<sup>8,9</sup> Note that this is the typical position of the pharmaceutical industry on medication use in lactation, as they are not required to evaluate medication safety in pregnancy or lactation and are concerned with liability issues.<sup>7,10</sup> Although many disease experts consider at least some biologics compatible with breastfeeding, it is acknowledged that there is still insufficient information available to fully guarantee their safety.<sup>6,11,12</sup>

## Comparison with Oral Immunosuppressive Agents in Lactation

It is important to note that some oral (nonbiologic) drugs traditionally used to treat moderate to severe autoimmune

conditions (e.g., methotrexate, cyclosporine, azathioprine) have potential safety concerns and monitoring requirements when used in lactation, with methotrexate being considered contraindicated by most references.<sup>13–15</sup> The PIANO registry followed the outcomes of women with inflammatory bowel disease through pregnancy and the postpartum period. The subjects used tumor necrosis factor (TNF) inhibitors (a class of biologic medication), a thiopurine (either azathioprine or 6-mercaptopurine), both a TNF inhibitor and a thiopurine, or neither medication. The infants exposed to both medication classes had a higher incidence of infection between 9 and 12 months compared with the unexposed group, but the infants exposed to only TNF inhibitors did not. It must be noted that detailed information on the extent and duration of breastfeeding in registry patients is not published, and medication exposure during pregnancy, not breastfeeding, was the primary research objective.<sup>16</sup>

### Counseling the Nursing Mother

It is imperative that the nursing mother has the necessary information to make an evidence-based, well-informed decision about breastfeeding her child and managing her own medical conditions. She must be aware of the potential consequences of not treating her autoimmune condition as well as the adverse effects of artificial feeding for both her infant and herself.<sup>17</sup>

Although no infant side effects have been reported during monotherapy with immunosuppressive biologics, the mother can monitor the child for signs and symptoms of infection or gastrointestinal irritation. There are currently no recommendations or requirements for laboratory monitoring of the infant during exposure to these medications.

It is important to note that women with autoimmune disorders may be less likely to breastfeed or to discontinue medication while breastfeeding, increasing the risk of disease flares.<sup>18,19</sup> Reasons for not breastfeeding cited by study patients included physician recommendation and fear of exposing their infants to medication transferred through milk.<sup>19,20</sup> Because of this, additional counseling and support on the importance of breastfeeding and maintaining maternal health should be provided. Dialogue and collaboration with other healthcare professionals (family physician, specialist, public health nurse, pharmacist, etc.) will likely be necessary to ensure continuity of care in regard to breastfeeding.

It is interesting to note that some autoimmune diseases, such as rheumatoid arthritis and Crohn's disease, are correlated with receiving artificial feeding in infancy.<sup>21–23</sup> Because these conditions are likely caused in part by genetic factors, the risks of depriving these infants of breastmilk should be carefully considered, especially because they have a first-degree relative (mother) with an autoimmune condition.

### Examples of Biologic Agents with Lactation Data

Adalimumab (Humira<sup>®</sup>; Abbvie, North Chicago, IL) is a monoclonal antibody that acts as a TNF inhibitor. It transfers into breastmilk in small amounts but is not likely absorbed by the infant. Most experts state that adalimumab is likely compatible with breastfeeding. Infant serum levels measured in two cases (at 8 weeks in one infant and 3 months in the other) were undetectable. No adverse effects or develop-

mental abnormalities have been reported in infants exposed to adalimumab monotherapy during breastfeeding.<sup>6,24</sup>

Anakinra (Kineret<sup>®</sup>; Sobi, Inc., Solna, Sweden) is a recombinant human interleukin-1 receptor antagonist. There is one case report of a woman breastfeeding her infant while using anakinra without any apparent adverse outcomes. Because interleukin-1 receptor antagonist naturally occurs in breastmilk, the risk of exposing a nursing infant to this medication is likely low.<sup>6,25</sup>

Certolizumab (Cimzia<sup>®</sup>; UCB Group, Brussels, Belgium) is a monoclonal antigen-binding fragment that acts as a TNF inhibitor. One infant was exposed both in utero and via breastmilk, with a serum certolizumab concentration of 1.02 mg/L at birth and 0.84 mg/L at 1 month postpartum. These decreasing levels imply that the infant received the medication while in utero only, rather than through breastmilk. Certolizumab was undetectable in breastmilk samples from the mother, and infant oral absorption would be unlikely even if it were present. No adverse effects or developmental abnormalities have been reported in infants exposed to certolizumab monotherapy during breastfeeding.<sup>6,26</sup>

Etanercept (Enbrel<sup>®</sup>; Amgen, Thousand Oaks, CA) is a fusion protein that acts as a TNF inhibitor. Even though etanercept is excreted in breastmilk (the relative infant dose is 0.07–0.2%), it is not orally absorbed by the infant. Note that in infants exposed to this medication in utero as well as via breastmilk, the serum levels decline as the postpartum period progresses. In one infant, the serum level was 21  $\mu\text{g/L}$  at 1 week postpartum and undetectable at 12 weeks postpartum despite continued breastfeeding, indicating that the 1-week serum value was measurable because of in utero exposure. As is to be expected, given the lack of absorption, no adverse events or developmental abnormalities have been reported in infants exposed to etanercept in breastmilk.<sup>6,10</sup>

Infliximab (Remicade<sup>®</sup>; Janssen Biotech, Horsham, PA) is a monoclonal antibody that acts as a TNF inhibitor. Most experts state that infliximab is compatible with breastfeeding. As with etanercept, absorption by the infant is unlikely despite some transfer into breastmilk (the relative infant dose is 0.3%). Serum levels in infants are either low or undetectable. In one infant exposed to infliximab during both pregnancy and lactation, maternal and infant serum levels were equal at 6 weeks postpartum, but the infant level declined over the next 7 weeks despite continued breastfeeding and maternal therapy. This suggests that the high infant serum level at 6 weeks was due to in utero exposure. No adverse effects or developmental abnormalities have been reported in infants exposed to infliximab monotherapy during breastfeeding.<sup>6,12</sup>

### Examples of Biologic Agents Without Lactation Data

Abatacept (Orencia<sup>®</sup>; Bristol-Myers Squibb, New York, NY) is an immunomodulating fusion protein that inhibits T cell activation.<sup>6,27</sup>

Golimumab (Simponi<sup>®</sup>; Janssen Biotech) is a monoclonal antibody that acts as a TNF inhibitor.<sup>6,28</sup>

Rituximab (Rituxan<sup>®</sup> [Genentech, South San Francisco, CA], MabThera<sup>®</sup> [Roche, Basel, Switzerland], or Zytux<sup>™</sup> [AryoGen, Tehran, Iran]) is a monoclonal antibody that induces B-cell destruction.<sup>6,29,30</sup>

Tocilizumab (Actemra<sup>®</sup> [Genentech] or RoActemra [Roche]) is an anti-interleukin-6 receptor antibody.<sup>6,31</sup>

Ustekinumab (Stelara<sup>®</sup>; Janssen Biotech) is an anti-interleukin 12/23 monoclonal antibody.<sup>6,32</sup>

There are no published human data on the use of the above medications in lactation. However, transfer into breastmilk would likely be low, and infant absorption unlikely, because they are high-molecular-weight proteins. Note that Dr. Thomas Hale, a leading expert on medication use during lactation, recommends greater caution with rituximab compared with other biologics, probably because of its antineoplastic uses. He advises that women do not breastfeed if they are less than 2 weeks postpartum or after receiving a dose, despite the unlikelihood of rituximab entering breastmilk in clinically relevant amounts.<sup>6</sup>

## Conclusions

Autoimmune disorders are common in women of child-bearing age, with many women requiring ongoing therapy to maintain remission and improve quality of life. Therefore, the use of biologics in lactation may be frequently encountered in clinical practice. Although the limited data available do suggest compatibility with lactation, more research is needed to definitively establish safety, in terms of both number of breastfeeding dyads studied and the length and detail of follow-up. Until more research is conducted, mothers must be encouraged to make well-informed decisions based on what evidence is available. The pharmacokinetic properties of these medications, which indicate that transfer into milk and absorption by the infant would be minimal, must be considered. Some sources currently advise using biologics in lactation “with caution,” particularly when the child is premature or a newborn.<sup>25,28,29,32</sup> It is indeed prudent to exercise caution, but this caution can take the form of careful monitoring of both mother and infant rather than withholding effective treatment from the mother or exposing both the mother and infant to the risks of artificial feeding. Conflicting medical opinions and a paucity of safety data complicate the decision-making process. Therefore, these women require individualized and comprehensive support in managing both their medical conditions and their nursing relationships with their children, in order to ensure optimal maternal health and breastfeeding outcomes.

## Disclosure Statement

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