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Anti-VEGF Therapy in Pregnancy and Breastfeeding

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Introduction

Anti-vascular endothelial growth factor (VEGF) is the mainstay of treatment for several visually debilitating diseases and is considered the standard of care for a number of conditions which may affect younger patients, including women of childbearing age. These commonly include, but are not restricted to, diabetic macular edema (DME), proliferative diabetic retinopathy (PDR) and myopic choroidal neovascularization (CNV). As in other areas of medicine, pregnant and breastfeeding women are often excluded from clinical trials due to the unknown side effect profile of new drugs. This lack of evidence regarding the safety of anti-VEGF agents in pregnancy and breastfeeding introduces challenges for clinicians seeking to counsel these patients, particularly because anti-VEGF injections may be often used for an extended period of time, depending on the nature of the retinal disease. As a precaution, anti-VEGF injections are generally not recommended for women who are either pregnant or breastfeeding, given that they are considered Category C drugs and there is limited data regarding their excretion in human breast milk.[1,2] Therefore, treatment of this group of patients is typically managed on a case-by-case basis, balancing the potential patient benefits with safety concerns for the infant.

Pregnancy can indeed exacerbate or induce retinal conditions that may require treatment with anti-VEGF drugs.[3] Each treatment decision must be individualized, taking into consideration the importance of the drug to the mother. In cases of PDR, laser photocoagulation can be safely performed. Focal laser photocoagulation may also be used to treat cases of non-center involving diabetic macular edema. As an alternative to anti-VEGF injections, intravitreal steroids can be used in cases of center-involving DME, macular edema secondary to retinal vein occlusions, or inflammatory conditions. However, the use of intravitreal steroids may also introduce their own risks of premature cataract formation and high intraocular pressure in this typically young patient population. Finally, other diseases, such as myopic CNV, currently have anti-VEGF injections as the mainstay of treatment.

There is evidence that anti-VEGF drugs reach the systemic circulation following an intravitreal anti-VEGF injection.[4] Once in the bloodstream, these medications become susceptible to reaching the breast milk - similar to other molecules, drugs and antibodies that are present in the mother's bloodstream and are known to cross into the breast

milk. The exact mechanism of how anti-VEGF drugs cross from the bloodstream into the breast milk remains unknown. Multiple variables likely play a role, including drug lipophilicity, molecular size and the drug level in the mother's blood.

Different anti-VEGF drugs have different systemic exposures amidst these molecules rapidly reaching the bloodstream after an intravitreal injection.[4] Among the anti-VEGF drugs that are most commonly used, bevacizumab, ranibizumab and aflibercept, systemic exposure following an injection has been shown to be highest with bevacizumab and lowest with ranibizumab.[4] In fact, following three monthly injections of each drug, there is no drug accumulation between the first and third doses of ranibizumab, as opposed to persistent accumulation observed with aflibercept and bevacizumab.[4] In addition, both intravitreal bevacizumab and aflibercept result in significant plasma VEGF suppression, with aflibercept demonstrating the greatest suppression levels.[4] In contrary, intravitreal ranibizumab results in mostly unchanged systemic VEGF levels.[4] Based on these results observed in the general population, it may be reasonable to assume that ranibizumab could be a safer option of intravitreal anti-VEGF drug to be used in the setting of pregnant and nursing patients.

Pregnancy

It is known that VEGF is involved in the maintenance of fetal and placental vasculature during pregnancy, and that reduced VEGF levels can lead to defective embryogenesis and even fetal loss.[5,6] In addition, because of the effect of VEGF on blood pressure regulation, anti-VEGF drugs can potentially be associated with maternal pre-eclampsia.[7] Therefore, the use of anti-VEGF drugs during pregnancy is concerning due to the potential risks of maternal and fetal complications.

In a literature review compiling 20 cases of women who had been administered either bevacizumab or ranibizumab injections during pregnancy, the majority of reports showed cases of a single anti-VEGF injection used throughout various periods of gestation, including the first trimester, in which pregnancy continued uneventfully without any fetal or maternal complications.[8] Three miscarriages and one case of pre-eclampsia were reported. In all three cases of miscarriage, a single injection of bevacizumab had been administered up to five weeks of gestation; two miscarriages occurred within ten days following injection in women with no risk factors. Although it is challenging to determine a causative correlation between an anti-VEGF injection and miscarriage, the short ten-day interval between both events raises a suspicion. The other case of miscarriage occurred two months post-injection in a mother with a high-risk age factor for pregnancy loss. Regarding the case that developed pre-eclampsia, this mother had additional cardiovascular risk factors and a causative effect was deemed to be less likely.

As a result of the lack of strong clinical evidence when it comes to the use of intravitreal anti-VEGF drugs in pregnant women, it is important to provide thorough patient counselling, explain the risks and benefits of this treatment, and discuss the existing findings in the literature. A personalized decision taking into consideration the risk of vision loss in the mother, along with the patient's gestational period and anticipated number of repeat injections, is recommended.

Breastfeeding

VEGF-A is a molecule that is naturally present in high concentrations in the breast milk.[9-12] It is known to regulate local mammary gland development in the nursing mother, and it is an essential growth factor in infancy. VEGF-A plays an important role in the development of the infant's digestive system, as well as in neurogenesis, renal medullary microcirculation expansion, lung angiogenesis and alveolarization.[12-16] Infants receiving anti-VEGF injections for retinopathy of prematurity (ROP) have been found to have higher rates of neurodevelopmental impairment when compared to preterm infants undergoing laser treatment for the same.[14] This finding raises a concern that similar effects may be observed in infants who ingest breast milk containing anti-VEGF, in the event that anti-VEGF enters the infant's systemic circulation and causes suppression of VEGF-A systemically.

A small number of case reports have explored the issue of anti-VEGF excretion during breastfeeding. Initial reports of patients receiving intravitreal bevacizumab found no transfer of anti-VEGF into the breast milk, although a reduction of 35% in breast milk VEGF-A levels was observed two weeks following bevacizumab injection.[17] Conversely, a different clinical study that included nursing patients undergoing injections with ranibizumab and aflibercept demonstrated that both drugs were excreted into the breast milk.[18] Additionally, there was a corresponding reduction in VEGF-A levels in the breast milk. In this case series, a 37-year-old treatment-naïve woman with myopic CNV underwent injections with ranibizumab following 16 months of breastfeeding. She discontinued

breastfeeding and did not pump her breast milk outside of study visits. Ranibizumab was first detected on Day 3 post-injection, with levels increasing over time until Day 28. There was a decrease in VEGF-A levels in the breast milk on Day 1 onward. The second patient was a 37-year-old woman who continued to regularly breastfeed while receiving ranibizumab injections for myopic CNV. Interestingly, ranibizumab levels in her breast milk remained under the assay's detectable threshold. It was hypothesized that the conflicting findings between these two patients could have been related to the patient's respective breastfeeding status. In the patient who discontinued breastfeeding, the free drug that continued to reach the breast milk most likely continued to accumulate for several days, accounting for the increasing drug levels observed over time. Conversely, in the second patient, who continued to regularly breastfeed, all the samples showed drug levels below the assay's detectable threshold, most likely because the drug in the breast milk was constantly excreted and ingested by the infant, and never accumulated sufficiently to a point above the assay's threshold level. The third patient was a 24-year-old treatment-naïve woman who was administered aflibercept for DME and elected not to breastfeed. Breast milk could only be pumped on Days 1 through 4 post-injection, after which no further breast milk was produced. Aflibercept was first detected in the breast milk on Day 4 post-injection, and VEGF-A was found to be decreased from Day 1 onward.

In light of the small number of cases in the literature, it is challenging to draw definite conclusions regarding the clinical impact of anti-VEGF injections during breastfeeding. However, these reports have provided evidence that anti-VEGF agents can be excreted into the breast milk and can consequently reduce the local levels of VEGF-A. However, the potential impact of ingesting breast milk with reduced VEGF-A levels, that also contains anti-VEGF drug, remains unknown. Another important question is whether or not ingested anti-VEGF drugs are actually transferred into the bloodstream of the breastfed infant and whether, in turn, VEGF is found to be systemically suppressed in the infant.

Our most current clinical study focused on investigating these questions, as the key concern is the effect anti-VEGF drugs present in the breast milk might have on the infant. Our additional objective was to test a breastfeeding strategy that could potentially minimize the infant's exposure to anti-VEGF drugs present in the breast milk, which might allow mothers to safely receive injections. Our breastfeeding protocol involved a three-day "pump and dump" strategy in which the nursing mother continuously pumped and discarded her breast milk for three days following an injection, then resumed breastfeeding her infant on demand after the third day. Preliminary results of this research suggest that this strategy appeared to minimize the infant's exposure to the drug: ranibizumab levels in the breastfeeding infant's serum remained undetectable and plasma VEGF-A levels remained similar to those encountered in control infants. Therefore, a three-day "pump and dump" strategy may be a feasible and possibly safe option for breastfeeding patients requiring anti-VEGF therapy.

Conclusion

Performing a large-scale clinical study on this topic is extremely challenging, as this clinical scenario does not commonly present itself. However, every retinal specialist, and perhaps some comprehensive ophthalmologists, will most likely confront a similar scenario at one point during their career. With these small studies as the only evidence currently available in a setting of high clinical relevance of anti-VEGF therapy, their results may be extremely helpful in the discussion that physicians may have with this patient cohort.

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