International Journal of Women's Dermatology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Update on biologic safety for patients with psoriasis during pregnancy

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 6 December 2016
Accepted 16 December 2016
Available online xxxx

Keywords:
psoriasis
pregnancy
lactation
biologic agents
TNF-alpha inhibitors

ABSTRACT

Biologic agents have become more common to treat patients with psoriasis, but concerns about their effect on pregnancy and lactation often preclude this treatment during these time periods. During the past decade, we have gained a much better understanding of the course of psoriasis during pregnancy and the safety of the use of biologic agents during pregnancy and lactation. Under certain circumstances, biologic agents can be considered appropriate treatment options for patients who are pregnant or lactating.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder. Psoriasis prevalence rates are estimated between 1.5% and 2% worldwide, and more than 7.2 million people are affected in the United States alone (Jacobson et al., 2011; Rachakonda et al., 2014). The average age of female patients at the time of disease onset is 28 years, which means that many of these patients with psoriasis are of childbearing potential (Tauscher et al., 2002).

Over the past decade, we have seen the emergence of biologic agents as a mainstay of treatment for patients with psoriasis. In 2013, approximately 25% of patients with psoriasis were treated with biologic agents and primarily with tumor necrosis factor-alpha (TNF-alpha) inhibitors such as adalimumab and etanercept (Armstrong et al., 2013). Today, newer and even more effective biologic therapies with more targeted mechanisms of action are available to patients. Thus, it is expected that most dermatologists will encounter female patients with psoriasis who are pregnant or desire to become pregnant while treated with a biologic agent. Data on this subject are limited but expanding, and dermatologists who have an understanding of the clinical course of psoriasis and the impact of biologic agents during pregnancy will be better equipped to weigh the risks and benefits of treatment and counsel patients appropriately.

Psoriasis and pregnancy

Pregnancy is marked by complex maternal hormonal and immune system changes. During pregnancy, the maternal immune system shifts from a T helper (Th) cell 1 to a Th2 response. With this shift, certain Th2-mediated diseases such as lupus erythematosus worsen during pregnancy (Ruiz et al., 2014). Other T cell subsets that are related to autoimmune diseases include Th17 and T regulatory (Treg) cells. A recent review article found a greater ratio of Th17 to Treg cells in patients with pregnancy complications and autoimmune diseases and a reversal of this ratio in patients who had a successful pregnancy with a tolerance to self-antigens (Figueiredo and Schumacher, 2016).

Psoriasis is thought to be a primarily Th17-mediated disease with some Th1 involvement and since both of these cells are downregulated during pregnancy, a patient's disease status can ameliorate during pregnancy. Psoriasis tends to improve for approximately half of patients, but an equal number of patients report no change or worsening of their psoriasis during pregnancy (Bobotsis et al., 2016; Murase et al., 2005). Additionally, the majority of patients with psoriasis report immediate postpartum disease flares (Murase et al., 2005).

Psoriasis comorbidities such as diabetes, metabolic syndrome, cardiovascular disease, and depression may also increase the risk of negative birth outcomes. A prospective cohort study of pregnant women with psoriasis compared with pregnant women who had no autoimmune disease found that patients with psoriasis were

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http://dx.doi.org/10.1016/j.ijwd.2016.12.003

more likely to smoke during the first trimester of pregnancy, be overweight or obese, and have a diagnosis of depression. These patients were also less likely to use prenatal vitamins or folate supplementation at the time of conception, and such modifiable risk factors could increase the risk for adverse birth outcomes (Bandoli et al., 2010).

Pregnancy outcomes are generally poorer in patients with psoriasis. One study that was presented in 2012 at the European Academy of Dermatology and Venereology found that women aged 35 years and older with psoriasis had significantly lower pregnancy rates and live birth rates compared with disease-free control patients (Powers, 2012). Studies that analyzed pregnancy in patients with psoriasis have presented conflicting data with regard to poor pregnancy outcomes such as preterm birth, low birth weight, recurrent miscarriage, and increased cesarean delivery, with some studies supporting and others refuting these findings (Ben-David et al., 2008; Lima et al., 2012; Yang et al., 2011). However, a recent review of psoriasis and adverse pregnancy outcomes concluded that more recent literature suggested a link between psoriasis disease severity, pregnancy, and the development of adverse outcomes. The authors postulated that immune system dysregulation in psoriasis likely leads to poorer outcomes in pregnancy (Bobotsis et al., 2016).

Fetal exposure to biologic agents during pregnancy

Exposure of the fetus to biologic agents during pregnancy depends on the transport across the placenta. Immunoglobulin G (IgG) is the only major class of antibody that is transported across the human placenta. Fetal levels of IgG in umbilical venous blood are low in the first two trimesters of pregnancy and do not surpass maternal levels of IgG until the beginning of the third trimester when active transport of the IgG molecules across the placenta increases rapidly (Chambers and Johnson, 2012). Transport of IgG is facilitated by the neonatal Fc receptor (FcRn) on the placenta. Of the four subclasses of IgG (G1-G4), IgG1 is the most effectively transported followed by IgG4, IgG3, and IgG2, respectively (Wakefield et al., 2011). Adalimumab and infliximab are both IgG1 immunoglobulins. A prospective study of 80 patients with inflammatory bowel disease (IBD) who were treated with adalimumab and infliximab found an inverse correlation between time of last exposure to drug during pregnancy and umbilical drug concentrations in the infant (Julsgaard et al., 2016). Etanercept is a fusion protein that also contains an IgG1 Fc portion but with less transplacental transport than adalimumab or infliximab (Kurizky et al., 2015).

Certolizumab differs from other biologic agents because it is a pegylated antigen-binding fragment (Fab) antibody that lacks an Fc region. Without this Fc region, it cannot be actively transported by the FcRn receptor on the placenta and thus, results in minimal placental transmission (Wakefield et al., 2011). A case series of 13 patients with rheumatic disease who were treated with certolizumab during late pregnancy showed measurements of certolizumab in the cord blood between undetectable and 1 μg/ml compared with average maternal plasma levels of approximately 33 μg/ml (Förger et al., 2016). This suggests that certolizumab may be used as a treatment during late gestation without potential exposure to the newborn. Of note, certolizumab is only approved by the U.S. Food and Drug Administration (FDA) for the treatment of psoriatic arthritis but results from randomized, controlled Phase II studies have shown very good efficacy in patients with psoriasis (Reich et al., 2012).

This information is clinically significant for both the mother and fetus. Ideally, patients would discontinue treatment with biologic medications prior to planned pregnancies but for many patients with psoriasis, this situation is impractical and may not be necessary (Horn et al., 2009). Because of the minimal placental transport of maternal antibodies during the first two trimesters of pregnancy, treatment of patients with anti-tumor necrosis factor (TNF) alpha biologic medications is generally considered safe during the first half of pregnancy (Förger and Villiger, 2016). Recommendations for the use of anti-TNF therapy in the treatment of patients with IBD endorse discontinuation of TNF-alpha inhibitors at week 22-24 of pregnancy, but the rheumatology literature suggests safely continuing therapy up until Week 30 of pregnancy (Levy et al., 2016; van der Woude and Kanis, 2016). Newer consensus statements from the Canadian Association of Gastroenterology that were published in March 2016 state that women with a low-risk of IBD relapse and a compelling reason to discontinue treatment with anti-TNF therapy should stop at Weeks 22 to 24 but all other women with IBD who are treated with anti-TNF therapy are recommended to continue anti-TNF treatment throughout the pregnancy (Nguyen et al., 2016). These recommendations were classified as a "strong recommendation" on the basis of low-quality evidence but the assumption was that the risks of treatment with anti-TNF therapy outweighed the risk of an IBD relapse with subsequent effects on both the mother and fetus during pregnancy.

Patients with psoriasis who continue treatment with biologic agents during their pregnancy and particularly into the third trimester should be informed of the potential for an impaired immune response in their newborn infants. One case report of a death due to disseminated Bacillus Calmette-Guérin (BCG) infection following live BCG vaccination in an infant borne to a mother receiving infliximab during pregnancy, caused significant and warranted alarm (Cheent et al., 2010). Multiple studies have documented that levels of anti-TNF agents are detected in infants at birth and decline thereafter (Chambers and Johnson, 2012); however, a few studies noted that drug clearance could take up to 1 year after birth (Julsgaard et al., 2016). Infliximab clears more slowly than adalimumab (Julsgaard et al., 2016). Therefore, the administration of live vaccinations should be avoided in newborns with exposure to TNF-alpha agents for at least 6 months after delivery but inactive vaccinations can follow the standard schedule as recommended by the Centers for Disease Control and Prevention (CDC).

General safety of biologic agents during pregnancy

Most of the data on biologic agents and pregnancy come from the gastroenterology and rheumatology literature because TNF-alpha inhibitors are most commonly used to treat patients with IBD and rheumatoid arthritis. Because pregnant women are commonly excluded from clinical trials, large, controlled studies of TNF-alpha inhibitors and newer biologic agents, such as ustekinumab (IL-12/23 inhibitor), secukinumab (IL-17 inhibitor), and ixekizumab (IL-17 inhibitor), are lacking. Most of our limited observations come from data from animals, case reports or case series, small retrospective studies, and, most recently, surveillance registries that collect outcomes from pregnant patients who are treated with biologic agents. However, these registries are subject to bias because those who experience anomalies or adverse outcomes may be more likely to report such events.

Investigations into the role of TNF-alpha in embryogenesis in TNF-alpha knockout mice showed that TNF-alpha may play a role in the prevention of structural anomalies by either activating defense mechanisms that protect the embryo from harmful maternal stimuli or stresses or signaling for apoptosis if overwhelming detrimental signals occur (Toder et al., 2003).

In contrast, concern about the increased risk of congenital malformations, preterm birth, low birth weight, and spontaneous abortions have been raised about treatment with TNF-alpha inhibitors. For reference, according to the FDA, the risk of major birth defect is 2% to 4% and the rate of miscarriage is 15% to 20% in the U.S. general

Please cite this article as: Porter ML, et al, Update on biologic safety for patients with psoriasis during pregnancy, International Journal of Women's Dermatology (2016), http://dx.doi.org/10.1016/j.ijwd.2016.12.003