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Short Report

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Ustekinumab Drug Levels in Maternal and Cord Blood in a Woman With Crohn's Disease Treated Until 33 Weeks of Gestation

Catherine R. Rowan,[a] Garret Cullen,[a] Hugh E. Mulcahy,[a] Denise Keegan,[a] Kathryn Byrne,[a] Deirdre J. Murphy,[b] Juliette Sheridan,[a] Glen A. Doherty[a]

[a]Centre for Colorectal Disease, St Vincent's University Hospital and School of Medicine, University College Dublin, Dublin, Ireland [b]Academic Department of Obstetrics and Gynaecology, Coombe Women and Infants University Hospital and Trinity College, University of Dublin, Dublin, Ireland

Corresponding author: Dr Catherine Rowan, MB BCh BAO, MRCPI, Centre for Colorectal Disease, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland. Email: C.Rowan2@st-vincents.ie

Abstract

A 35-year old woman with ileocolonic, perianal, and vulval Crohn's disease was treated with subcutaneous ustekinuamb [USK] throughout pregnancy. Dose intervals were shortened from 6-weekly to 4-weekly to maintain clinical remission. The last dose of USK was administered at 33 weeks of gestation, and a healthy baby boy was delivered by caesarean section at 37 weeks. Maternal trough USK levels remained stable during pregnancy. Cord blood USK levels were nearly 2-fold higher than contemporaneous maternal serum levels. To our knowledge, this is the first report of maternal and cord USK levels in a patient with Crohn's disease.

Key Words: Ustekinumab, pregnancy, trough concentrations

1. Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] that is becoming increasingly common.[1] Typically, CD affects young people of reproductive age and higher rates of voluntary childlessness have been documented in patients with IBD.[2] Active IBD can affect fertility and negatively impact on pregnancy outcomes.[3] Current guidelines recommend optimising disease control and medications before conception, and it is often advised that patients continue anti-tumour necrosis factor [TNF] medications.[4,5] Previous studies found that approximately 20% of patients with IBD and active reproductive wishes require treatment with anti-TNF agents.[6] Therefore, the safety of biologic therapies in pregnancy is a pertinent clinical issue.

Ustekinumab [USK] is a humanised IgG monoclonal antibody to the p40 subunit common to both IL-12 and IL-23.[7] USK has been available for the treatment of moderate-severely active plaque psoriasis for several years. Following the publication of Phase 3 data,[8] it has recently been approved for the treatment of patients with moderate-severely active Crohn's disease, who have had an inadequate response, loss of response, or are intolerant of conventional therapy, including anti-TNF agents. However, in real-world practice, USK has been used in an open-label fashion to treat CD for some time. Despite this there remain limited data regarding the use of ustekinumab in pregnancy, and much of the data pertains to patients with psoriasis.

IgG monoclonal antibodies, such as infliximab [IFX], have been detected in cord blood at higher concentrations that in maternal serum, and therapeutic levels of IFX have been recorded in the infants of women treated during pregnancy.[9,10] There are currently no data regarding USK levels in pregnancy. In this case we describe maternal trough USK levels during pregnancy and at the time of delivery, as well as detectable USK in cord blood.

2. Case Report

A 35-year old woman with a 19-year history of ileocolonic, perianal, and vulval Crohn's disease requiring colectomy was treated with subcutaneous [sc] ustekinumab [USK]. The patient had previously had a severe infusion reaction to IFX and a loss of response

to adalimumab [ADA]. Induction was provided exclusively by sc USK with 180 mg sc at Week 0 followed by 90 mg at Weeks 1, 2, and 8. The patient was not on concomitant immunomodulator therapy at the time of induction. Baseline albumin and C-reactive protein [Crp] were 32 g/L [normal > 35 g/L] and 8 mg/L [normal < 5 mg/L], respectively, and faecal calprotectin via the patient's stoma was 636 µg/g [normal < 15 µg/g].

Maintenance dosing was initially given as 90 mg sc every 6 weeks; this was escalated, based on clinical grounds and elevated C-reactive protein [39 mg/L], to 90 mg sc every 4 weeks. Following dose escalation there was an improvement in symptoms and biochemical markers. Before treatment with USK, the patient had undergone two unsuccessful cycles of in-vitro fertilisation [IVF]. She conceived her first child without the use of assisted reproduction, following 4 months of therapy. She continued USK 90 mg 4-weekly throughout her pregnancy, without the need for steroids, immunomodulators or further dose optimisation. The last dose of USK was administered at 33 weeks of gestation.

Trough levels of USK were prospectively collected at the time of induction and throughout pregnancy. USK concentrations were measured by an automated enzyme-linked immunosorbent assay [ELISA] [Sanquin Diagnostic Services]. Serum and cord blood samples were collected at the time of delivery, which was 4 weeks after the last dose of USK was administered.

By the completion of induction therapy at Week 8, the trough USK level was 2.5 µg/ml. Conception occurred at approximately Week 16 of treatment. The median USK trough level during the pregnancy was 4.5 µg/ml (interquartile range [IQR] 3.43–5.15 µg/ml). The median USK trough levels during the first, second, and third trimester were 3.3 µg/ml [range 1–3.8 µg/ml], 5 µg/ml [range 4.7–5.2 µg/ml], and 5.1 µg/ml [range 4.3–5.9 µg/ml], respectively. There was no significant change in trough levels over the course of the pregnancy [$p = 0.43$; Friedman's Test]. At the time of delivery, the serum USK level was 4.3µug/ml and the cord blood USK level was 8.0 µg/ml [Figure 1].

The pregnancy was uneventful, with the patient remaining in clinical remission (HarveyBradshaw Index [HBI] < 4). An elective caesarean section was planned for 38 weeks of gestation, in collaboration with her obstetrician. Delivery was performed by caesarean section at 37 weeks due to spontaneous rupture of membranes. A healthy boy, weighing 2948 g and without congenital abnormalities, was delivered. There were no neonatal or maternal complications. The patient resumed USK treatment 4 weeks postpartum and continues to respond to therapy.

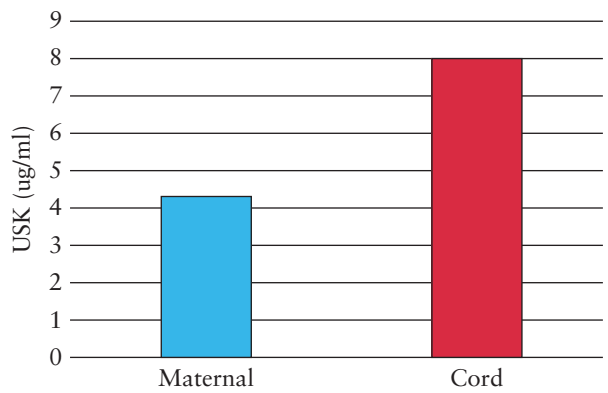

Figure 1. Maternal serum ustekinumab levels compared with cord blood ustekinumab levels at time of delivery [37 weeks of gestation].

3. Discussion

Pregnancy in patients with IBD is an evolving area. It is now recognised that disease activity is associated with higher rates of adverse outcomes, such as low birthweight and preterm labour.[11] Current guidelines advocate that patients be in remission at the time of conception and throughout pregnancy.[4] However, many patients require the use of biologic agents to achieve and maintain disease remission, and the safety of these medications in pregnancy has not been formally studied in randomised controlled trials. Registry data have not demonstrated an increased risk of congenital defects or other adverse outcomes in infants born to mothers requiring biologic therapy during pregnancy,[12] despite the fact that anti-TNF medications such as IFX are detectable in cord blood.[9] Indeed, IFX and ADA levels in the infant often exceed maternal anti-TNF levels.[13] The effects of pregnancy on the pharmacokinetics of anti-TNF agents have recently been reported and show a significant increase in maternal IFX levels during pregnancy but stable ADA levels overall.[14] Therapeutic drug monitoring during pregnancy may help limit fetal exposure while maintaining therapeutic maternal drug levels, a parameter yet to be established for USK.

USK is a humanised IgG1 monoclonal antibody and, like IFX, its active transplacental transport is facilitated by the fetal Fc receptors. IgG1 is preferentially transported compared with IgG2-4. The fetal Fc receptors are first detected at 14 weeks of gestation, and transplacental transport of IgG1 peaks in the third trimester.[15] USK is a relatively new addition to the IBD portfolio, and data regarding its use in pregnancy are very limited. Animal studies in cynomolgus macaques treated with supra-therapeutic doses of USK during gestation did not highlight any concerns regarding adverse maternal or fetal effects. USK was detectable in macaque infant serum up to 3 months of age.[16]

In humans, limited registry data are available via PSOLAR. PSOLAR is a multicentre, longitudinal, observational study of the long-term safety outcomes of psoriasis patients receiving biologic agents, including USK. A small number of pregnancies have been recorded on this registry. The outcomes of women specifically exposed to USK are not detailed, but pooled analysis suggests similar rates of live births, congenital abnormalities, and spontaneous abortions in women treated with biologic agents compared with the US general population.[17] In patients with CD, there are only three case reports of patients exposed to USK during pregnancy. One case of miscarriage at 8 weeks of gestation is described, in which treatment with USK was stopped once pregnancy was confirmed. The patient continued in remission following treatment cessation.[18] Of the remaining two cases, one patient was treated with USK, 90 mg 12-weekly, until 33 weeks of gestation for CD and paradoxical psoriasis, and the other received USK and concomitant azathioprine throughout pregnancy.[19,20] No adverse outcomes were documented in either case.

This is the first case report describing USK trough levels during pregnancy and in cord blood. Overall, USK levels remained stable throughout pregnancy. Cord levels were nearly 2-fold higher than maternal serum levels. Further studies are needed to clarify the therapeutic level of USK and the effect of pregnancy on its pharmacokinetics. Whereas there were no adverse events noted in this case, there remain limited data regarding the use of USK in pregnancy and its effect on offspring. With a growing number of patients of reproductive age being exposed to USK, it is critical to report experiences of its use in pregnancy, to optimise outcomes for both mother and child.

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Conflict of Interest

The authors have no conflict of interest.

Author Contributions

CR and GAD were involved in the concept of the study. CR, DK, and KB carried out the data collection and analysis. Sanquin Diagnostic Services performed the USK trough concentration measurements. CR, JS, and GAD drafted the report. DJM, GC, and HEM assisted in editing the final draft of the manuscript.

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