1. Do statins lower the risk of IBD?

Certain environmental factors and medications such as NSAIDs are associated with an increased risk of IBD. However, there are much fewer dietary or pharmacological products that are believed to be protective against IBD. Statins have received much attention recently due to their presumed anti-neoplastic effect. In addition, statins appear to have immunomodulator effects including decreased T-cell activation and cytokine production, which in vitro appear to be mediated through nuclear factor kappa B. These investigators studied the association of statin exposure with the onset of new cases of IBD in a large administrative database from the US. The IDV (Integrated Dataverse) database contains medical information and prescription claims from over 220 million unique patients including commercial and Medicare insurance plans. Patients with new onset IBD were identified using diagnostic codes and prescription for statins, as well as IBD-related medications using pharmacy dispensation data. Cases were compared to a matched cohort of patients who did not develop IBD during the same period. Comorbid conditions and particularly those associated with statin use - cardiovascular disease & hypertension- were also abstracted from the claims data. Following a heavy triage, 9,617 cases (new IBD diagnoses) and 46,665 controls were identified. Despite similar age, cases were more likely to be obese and have coronary and cerebrovascular disease compared to control patients. New onset IBD was associated with a significantly lower frequency of statin use (21% vs. 28%) with a similarly protective effect for both UC and CD. The strongest protective effect was seen against CD in patients who were older than 60, and did not appear to have a significant effect in patients younger than 50. All but two statin drugs had a protective effect, although the two exceptions are infrequently used and no dose response association was seen.

Comments: Despite the very large patient population included in the IDV database, the authors were only able to capture a relatively small number of incident IBD cases (10,000), whereas it is estimated that there are over 60,000 new IBD cases per year in the US. Thus, the results are likely subject to selection or validation bias. In addition, there is no information on smoking, family history, and health habits including changes in diet. Given the access to longitudinal medical data from a large number of subjects it is unclear why the authors did not take the opposite approach of studying the incidence of IBD among statin users vs. non-users. The fact that the protective role was seen mostly for Crohn’s in older subjects is particularly intriguing, again suggesting some form of bias from an unidentified confounder. One previous retrospective study failed to show a protective effect and 2 prospective studies showed no significant effect of statins on disease activity. Even if the results of this study were valid, the number needed to treat would be around 14, which is relatively modest for an uncommon condition for which individuals at high risk are difficult to identify. Although a definitive conclusion cannot be drawn regarding the effect of statins on IBD, further studies addressing potential in vitro mechanisms of action of statins on the immune system may be worthwhile.

2. Biologic drug levels in mothers and infants, and impact on outcomes in the first year of life

Although anti-TNF biologics are considered ‘former’ category B drugs, there is relatively little known about the pharmacokinetics and pharmacodynamics of these agents in pregnant females and their impact on the offspring. Both ADA and IFX are IgG1-based mAbs which are actively transferred by the placenta to the fetus, particularly during the 3rd trimester of pregnancy. The immunosuppression conferred by trans-placental transfer of anti-TNF biologics may increase the risk of infections or iatrogenic injury from administering live vaccines such as rotavirus. Investigators from Denmark, Australia, and New Zealand performed a prospective study in pregnant women with IBD who were recruited from tertiary hospitals over a period of 2 years, with the primary aim to determine drug pharmacokinetics in the mother and baby. 80 mother-baby pairs were available for analysis; the majority of patients (mothers) had Crohn’s disease (83%) and 55% were using IFX. The vast majority of patients (90%) were on standard dose of either ADA or IFX, and half were on combo therapy with a thiopurine. The majority were in remission at conception or during pregnancy. Half of the patients discontinued the biologic during the 3rd trimester - week 30 for IFX and 35 for ADA. Women with active disease before pregnancy were more likely to have active disease during pregnancy compared with those who were in remission. In addition, women who stopped the biologic early during pregnancy did not seem to have an increased risk of relapse compared with women who continued treatment throughout. There was a very low rate of pregnancy-related complications including congenital malformations, well within the expected range. At birth, cord blood and infant levels of both biologics were significantly higher compared with maternal serum levels (median ratio for ADA 1.21 and for IFX 1.97). There was a significant inverse correlation between the duration since the last dose of drug and cord blood concentration of both ADA and IFX. The median time for ADA clearance after birth in the infant was 4 months and for IFX it was 7.3 months, although the concentration of IFX was much higher at birth compared to ADA. Thus, the estimated mean half-life of ADA was 26 days compared with 33 days for IFX. The risk of any infection in the offspring in the first year of life was higher if their mothers received combo therapy compared with monotherapy during pregnancy. However, all infections were mild and resolved with antibiotics or conservative management. Continuing the biologic in the 3rd trimester did not increase the risk of infection.

Comments: Despite its small size, this is a very important study to help understand the pharmacology of biologic agents during pregnancy and the effect of exposure in-utero on post-partum outcomes in the offspring. It is interesting to see that infants of mothers treated with combo therapy had a higher rate of infections compared to those treated with biologic monotherapy, although the cord blood drug levels did not correlate with the risk of infection during the first year of life. This may suggest that the thiopurines may increase the risk of infection through an independent mechanism, although the number of cases was very small and there was no control group treated with thiopurines alone. As far as the comparison between the clearance of IFX and ADA, this is likely biased by the fact that the IFX dose is weight-based while ADA is “one size fits all”. Since there was an extremely broad range of body weights in mothers (BMI 17-42) and the authors did not mention if the IFX dose was steadily adjusted based on weight throughout pregnancy, the difference in the duration of detectable
drug between IFX and ADA in the infant may simply be a reflection of the dose and maternal serum levels and not pharmacokinetics. In fact, maternal serum IFX levels were consistently higher than ADA levels whether the drug was continued in the 3rd trimester or not. It is likely that other individual factors affect the drug clearance as well. What is certain is that the half-life of both biologics was 2-4 times longer in babies compared to mothers and this may be important in estimating a safe window for administering live vaccines. The fact that interrupting the biologic before the third trimester was not associated with an increased risk of flare may be due to selection bias, as only mothers with inactive disease were advised to discontinue the drug.