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Pregnancy Alters Pharmacodynamics of Anti-TNF Agents in Women With IBD

Amy Karon

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Blood levels of infliximab rose during pregnancy, while adalimumab levels remained stable, even after researchers accounted for changes in albumin, BMI, and C-reactive protein levels, according to a novel single-center study of 25 women with inflammatory bowel disease (IBD).

Furthermore, blood levels of both anti-tumor necrosis factor (TNF) agents varied considerably among patients, reported Dr. Cynthia Seow, a gastroenterologist at the University of Calgary. "We should consider therapeutic drug monitoring during the prepregnancy period in order to optimize the dose during pregnancy," she said. "Therapeutic drug monitoring may also be considered for pregnant women receiving infliximab in the second trimester to guide third-trimester dosing."

Active IBD during pregnancy increases the risk for relapse and preterm birth, Dr. Seow noted at the annual Digestive Diseases Week. Thus, infliximab and adalimumab are used to keep IBD in check during pregnancy, even though they cross the placenta and reach higher levels in the cord blood and newborn than in the mother (*Clin Gastroenterol Hepatol*. 2013;11[3]:286-292). "However, it is not known how pregnancy itself influences the pharmacokinetics of anti-TNF agents, nor the implications of this on prescribed dosing," said Dr. Seow.

Therefore, she and her colleagues analyzed blood samples from 25 women receiving stable maintenance anti-TNF therapy for IBD, who attended a median of three prenatal visits at the University of Calgary IBD Pregnancy Clinic. Fifteen women received infliximab during 15 pregnancies, and 10 women received adalimumab during 11 pregnancies. Infliximab levels were drawn at trough times, while adalimumab levels were usually drawn three days before the next injection. Blood samples were tested only after delivery, and anti-TNF doses were not adjusted during pregnancy.

The infliximab group included eight women with Crohn disease and seven with ulcerative colitis, while the adalimumab group included nine women with Crohn disease and one with ulcerative colitis. The treatment groups were similar in terms of age at diagnosis and pregnancy, time on anti-TNF agents, and average gestational age at delivery, which was 39.2 weeks (range, 38.1-40.2 wk) for the infliximab group and 38.4 weeks (range, 37.2-39.6 wk) for the adalimumab patients.

Median infliximab concentrations rose from 8.5 µg/mL in the first trimester to a peak of 21 µg/mL during the middle of the third trimester ($P = .04$), and then dropped to nearly preconception levels after delivery. "This change persisted irrespective of disease phenotype," Dr. Seow reported. Albumin levels correlated inversely with infliximab levels. In contrast, median adalimumab levels ranged between 8.6 and 12.2 µg/mL during pregnancy, dropped to 6.8 µg/mL after birth, and were unrelated to albumin levels.

BMI and C-reactive protein levels did not affect blood levels of either drug, and the researchers found no differences in pharmacokinetics in subgroups of patients who had only two blood draws, subtherapeutic drug levels, or consistently absent drug levels. Three patients had detectable antibodies during pregnancy, all of whom had a stable clinical course. "The antibody levels appeared to decrease as the pregnancy progressed, and then appeared to increase again after delivery," Dr. Seow said. She also noted that one-third of the infliximab group and

nearly half of the adalimumab group were receiving combination treatments for IBD, and their anti-TNF blood levels resembled those of patients on monotherapy.

The researchers did not test cord blood or blood samples from the newborns, but based on past evidence, fetal anti-TNF exposure has implications for current live vaccination recommendations in infants. "The long-term consequences of anti-TNF exposure remain unknown," Dr. Seow concluded.

Disclosures: *Dr. Seow disclosed ties with Janssen, AbbVie, Takeda, Shire, and Actavis.*

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Vascular Disease Linked to Sight Loss in Giant Cell Arteritis

Sara Freeman

People with giant cell arteritis (GCA) may be more likely to go blind if they have underlying vascular disease, according to an analysis of the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS). The results of the analysis showed that 7.9% of patients with this common type of vasculitis go blind in at least one eye within six months of diagnosis and that those with a history of peripheral vascular disease (PVD) could be at up to 10 times higher risk than those without additional vascular comorbidity.

"This is the first multinational study for patients with [giant cell arteritis], and it shows that blindness is a significant problem," said Dr. Max Yates of the University of East Anglia in Norwich, England, who presented the findings at the British Society for Rheumatology annual conference. Blindness was defined as complete visual loss rather than by a full ophthalmology assessment, so the findings probably underplay the problem in patients with some form of visual loss, he observed. Visual disturbance had been noted in 42.9% of the patients who were studied at the first clinic review.

"It is interesting that there is the association with vascular disease," Dr. Yates noted. "Perhaps we need greater vigilance in those people who already have a diagnosis of vascular disease [and] to really watch and monitor those people carefully for sight loss."

The DCVAS is an ongoing project designed to develop and validate new classification and diagnostic criteria for systemic vasculitis that can be used routinely in clinical practice and in clinical trials. So far, more than 3,500 participants older than 18 have been recruited from secondary care clinics, and 2,000 of those have a new or established diagnosis of vasculitis. The others have a similar presentation but an alternative diagnosis.

A total of 433 patients participating in the study were identified as having GCA with more than 75% diagnostic certainty, 93% of whom fulfilled the 1990 American College of Rheumatology (ACR) criteria for GCA and just over half (54%) had a positive temporal artery biopsy. Visual loss was recorded by completion of the Vasculitis Damage Index six months after diagnosis. Two-thirds of patients studied were women, the median age at diagnosis was 73, 40% had jaw claudication, 34% had lost weight, and 16% presented with a fever. In addition, 9.2% had diabetes; 3.2%, a prior stroke; and 2.5%, PVD.

In terms of predictive factors, baseline laboratory findings such as the presence of anemia, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, or platelet counts were not associated with sight loss. Dr. Yates noted that the baseline ESR range was 35-120 mm/h and the CRP ranged from 12 to > 100 mg/dL in the patients studied.

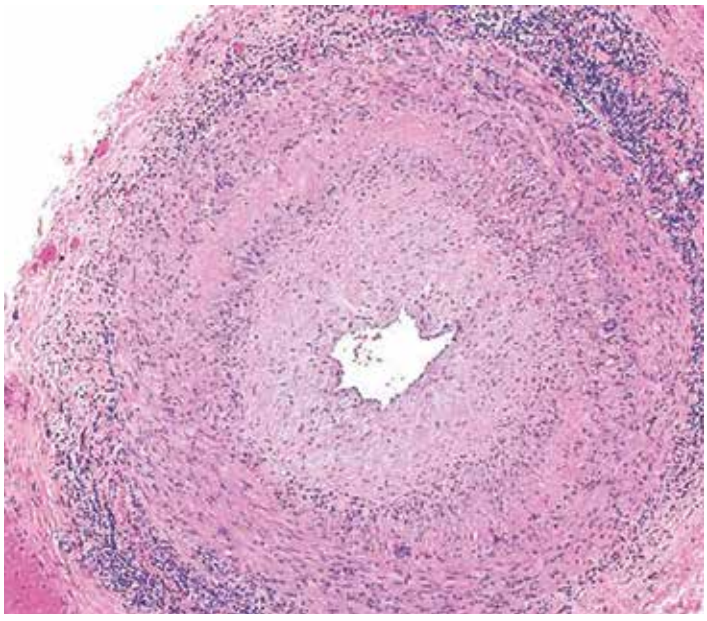
However, prior vascular disease was found to be predictive of later blindness. The odds ratio (OR) for being blind in at least one eye six months after a GCA diagnosis was 10.44 for PVD, with the 95% confidence interval (CI) ranging from 2.94 to 37.03. A prior diagnosis of cerebral vascular accident (OR, 4.47; 95% CI, 1.30-15.41) and diabetes (OR, 2.48; 95% CI, 0.98-6.25) also upped the risk for complete sight loss at six months.

Dr. Yates noted that patients were selected from multiple clinics across secondary care, so there should be better generalizability than in prior, single-center studies. However, there could be some residual referral bias. During discussion, it was men-

tioned that it would be helpful to know the rate of blindness in patients taking corticosteroids, as this was one of the major reasons for emergency rheumatology calls at one clinic, a delegate observed.

"Giant cell arteritis is really the major rheumatology emergency for practicing clinicians. We recently set up a rheumatology day service and usually get eight to 10 calls about it per day," the delegate said. "It's often said that once a patient is on any dose of corticosteroids, there is no risk of them going blind." There is a lot of angst about whether it is safe to use higher doses (60 mg vs 40 mg) and "it's important for us as clinicians to be able to reassure people."

Dr. Yates noted that a prospective trial would be needed to answer the question and that trials were planned. "We don't have any data on treatment," he said. "So we're unable to say whether steroids were started instantly or whether there was any improvement in the visual function of these people." Long-term complications would also be a factor to investigate, particularly in older people who have an increased risk for eye problems (such as cataracts) and could be at higher risk for visual problems if treated with steroids or other agents.



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Disclosures: *The DCVAS study is supported by the ACR and is funded by the European League Against Rheumatism and the Vasculitis Foundation. Dr. Yates reported that he had no relevant disclosures.*

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Pediatric and Adolescent Mental Health

➤Part 1: Diagnoses, drug prescribing vary widely

Whitney McKnight

A lack of psychiatrists only partially accounted for substantial variations in rates of mental illness diagnosis and prescriptions for psychotropic medications in practices nationwide, a study has shown. Although a lack of available specialty care was associated with significantly higher odds of a diagnosis or prescription, the colocation of mental health professionals or percentage of children in foster care treated in a practice did not fully explain the differences.

Among 294,748 children between ages 4 and 18, seen one or more times in 43 primary care practices nationwide, 15% received a mental health diagnosis between January 1, 2009, and June 30, 2014. Psychotropic medications were prescribed to 14%, reported lead researcher Stephanie L. Mayne of the Center for Pediatric Clinical Effectiveness at the Children's Hospital of Philadelphia (*Pediatrics*. 2016. doi:10.1542/peds.2015-2974).

The most common diagnosis was attention-deficit/hyperactivity disorder, at a rate of 1% to 16%. Differences in other diagnoses were "smaller, but still meaningful," at ranges of 1% to 8% for anxiety, 0% to 5% for depression, 0.2% to 3% for autism, 0% to 3% for conduct disorder, and 0% to 2% for oppositional-defiant disorder. Bipolar disorder was "uncommon," at less than 1%, Ms. Mayne and her associates reported.

The rate of children receiving any psychotropic medication was between 4% and 26%, while the pro-

VIEW ON THE NEWS

Consider integrating mental health support into patient medical home

The integration of mental health services into primary care is an important strategy for increasing access. Future studies that investigate variations in mental health care seen in the primary care setting can help us better understand the quality of this care and consistency with published guidelines.

Increased education and support for primary care providers is essential because they are at the frontlines of providing care to children with mental and behavioral health concerns. However, working together with specialty mental health providers is also important, as they are important partners in the early identification, diagnosis, and treatment of mental disorders. Education and consultation models, such as Child Psychiatry Access Programs, can significantly improve a primary care provider's capacity to care for children with mental health concerns in the medical home and to arrange for appropriate specialty mental health treatment when indicated.

Dr. Lee Savio Beers is the Medical Director for Municipal and Regional Affairs for the Child Health Advocacy Institute at Children's National Medical Center, the Director of the Washington, DC, Mental Health Access in Pediatrics (DC MAP) program, and an Assistant Professor of Pediatrics at George Washington University, Washington DC. *She had no relevant financial disclosures.*

portion of patients receiving two or more medication classes ranged from 1% to 12%. Prescription rates for specific medication classes also varied, from 4% to 18% for stimulants, 1% to 12% for antidepressants, 0.1% to 8% for α-agonists, and 0.1% to 5% for second-generation antipsychotics.

"Primary care providers' level of agreement with current guidelines, perceived self-efficacy in diagnosing or treating particular conditions, training, relationships with schools, and reimbursement from insurers might affect prescribing practices," Ms. Mayne and her associates wrote. "Even with colocation, barriers such as financial differences in reimbursement for medical and mental health services, difficulties with information sharing, differing expertise, and limited hours may impede integration."

Disclosures: *Dr. Alexander G. Fiks is an investigator for Pfizer; the other researchers had no relevant financial disclosures. This study was funded by the National Institutes of Health and the National Institute of Child Health and Human Development under the Best Pharmaceuticals for Children Act.*

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➤ Part 2: Disorders prevalent in young transgender women

Mary Ann Moon

Young transgender women have a prevalence of psychiatric disorders that is two to four times higher than the general population, according to a report published in *JAMA Pediatrics*.

"Improving access to culturally competent primary care, diagnostic screening, psychotherapy, and pharmacologic treatments, and retention in care in clinical community-based pediatric and young-adult medicine settings are urgently needed to address the adverse mental health and substance dependence disorders in this population," said Sari L. Reisner, ScD, of Boston Children's Hospital and Harvard Medical School, and his associates.

They assessed mental health using brief, structured, diagnostic interviews with 298 young transgender women participating in an HIV-prevention study in Boston and Chicago during a three-year period. The study participants, all ages 16 to 29 (mean age, 23), had been assigned male sex at birth but self-identified as woman, female, transgender woman, transfemale, male-to-female, or other identity on the transfeminine spectrum. All reported participating in high-risk sexual activity. The study population was urban and ethnically diverse: 49% black, 12.4% Latina, 25.5% white, and 13.1% other race/ethnicity. Seventy-two percent reported ever using cross-sex hormones and 21% had undergone gender-reassignment surgery.

A total of 42% of these study participants had at least one psychiatric disorder, and 20% had two or more mental health diagnoses. The prevalence of lifetime major depressive disorder was 35%, suicidality within the preceding month was 20.2%, generalized anxiety disorder during the preceding six months was 8%, PTSD during the preceding six months was 10%, alcohol dependence during the preceding year was 11%, and substance dependence during the preceding year was 15%. These findings suggest that stressors unique to gender transition, such as adverse processes in identity development, "may affect psychiatric health and well-being across adolescence and young adulthood" (*JAMA Pediatr.*

VIEW ON THE NEWS

Extraordinarily high rate of diagnoses

Dr. Reisner and his associates confirm what has already been consistently reported in the research literature: The prevalence of mental health diagnoses among transgender adolescents and women is extraordinarily high, and timely, appropriate care is imperative to help them achieve health and wellness.

What is different with this cohort is that the young transgender women were recruited from the community, rather than from a population of those with the resources to access transgender-specific health care. It is clear that mental health services are lacking and inaccessible to much of the transgender population. This is due in part to the limited number of professionals who are experienced in working with transgender youth. But it can also be attributed to the lack of clarity, among both mental health professionals and the scientific and medical community in general, regarding the complex nature of the transgender experience.

Dr. Johanna Olson-Kennedy is with Children's Hospital Los Angeles. She made these remarks in an editorial accompanying Dr. Reisner's report (*JAMA Pediatr.* 2016 March 21. doi:10.1001/jamapediatrics.2016.0155). *She reported having no relevant financial disclosures.*

2016 March 21. doi: 10.1001/jamapediatrics.2016.0067).

"Pediatric, adolescent, or young adult primary care providers may be a first resource for families needing education and support and play a critical role in supporting transgender youth, including screening for psychosocial problems and health risks, referring for gender-specific mental health and medical care, and providing advocacy and support," Dr. Reisner and his associates said. They added that clinicians "should familiarize themselves with current international guidelines for the provision of clinical care to transgender young people to best meet both medical and mental health needs of this at-risk population."

Disclosures: *This study was supported by the National Institute of Mental Health. Dr. Reisner and his associates reported having no relevant financial disclosures.*

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