ACR Reproductive Health Summit on the Management of Pregnant and Lactating Women with Autoimmune Diseases

Kathryn Dao, MD; John J. Cush, MD; Arthur Kavanaugh, MD and Michael Weisman MD

On January 10, 2014, a Reproductive Health Summit on Autoimmune Diseases convened in Washington, D.C. The two-day event, organized by the American College of Rheumatology (ACR) Drug Safety Committee, included presentations by representatives from the Food Drug Administration (FDA), the National Institute of Health (NIH), the National Institute of Child Health and Human Development (NICHD), experts in obstetrics, maternal and fetal medicine, pediatrics, rheumatology, gastroenterology, dermatology, as well as patient support and advocacy groups. The idea for the Reproductive Health Summit arose from discussions at the 2012 ACR Drug Safety Summit (see DSQ Aug 2012). At that meeting, drug safety during pregnancy and breastfeeding were recognized as being among the top safety issues concerning both patients and rheumatologists, and it was considered important enough to dedicate another meeting specifically to this topic. Over the ensuing year and a half, plans for this summit were developed by ACR Drug Safety subcommittee co-chairs Drs. Michael Weisman and Artie Kavanaugh, DSC members and Dr. Jack Cush. Herein we present a brief summary of the information presented during the meeting.

The meeting opened with discussions led by Drs. Larissa Lapteva and Sally Seymour from the FDA, who provided a view of the regulatory challenges and forthcoming labeling changes that will address pregnancy and lactation. The FDA recognizes the immense knowledge deficits in drug safety and reproductive health, particularly in autoimmune diseases where the scope of changes in immunity is broad and clinical trials on pregnant and breastfeeding women are lacking. Most of what is known is limited and is based on observations from incidental pregnancies while on drug. The coupling of pregnancy with different autoimmune diseases poses a challenge for physicians and researchers as pregnancy alters disease pathophysiology and drug metabolism, and the disease and drug have unpredictable effects on the unborn child. In addition, pregnant and lactating women have typically been excluded from drug trials due to ethical concerns; they are considered a "vulnerable" population. Hence, current FDA pregnancy drug categories "A", "B", "C", "D", and "X" are based on animal data, limited registry information, and case series/reports. These labels are often confusing and do not fully disclose the risks and benefits of drug exposure during pre-conceptual planning, pregnancy, and lactation. The idea that drug safety in pregnancy is a continuum from X to A is not correct; these categories generally relate to the presence or absence of human or animal data. Notably, 90% of pregnant women take 1 or more prescription medicines and about half take at least 4 medications during pregnancy. The FDA understands the urgency to provide consumers and prescribers with usable information and is committed to work on updating the labels and to improve communication of risk. Furthermore, under the FDA Amendments Act of 2007, the FDA now is requiring pharmaceutical companies to conduct post-marketing trials on pregnant and lactating women and formulate risk evaluation and management strategies (REMS). The NIH and NICHD are interested in collaborating and promoting research in pregnant women and children with autoimmune diseases in basic, translational and clinical research, focusing on drug pharmacokinetics (PK), drug metabolism, disease pathophysiology and drug metabolism, and the disease and drug have unpredictable effects on the unborn child. In addition, pregnant and lactating women have typically been excluded from drug trials due to ethical concerns; they are considered a “vulnerable” population. Hence, current FDA pregnancy drug categories “A”, “B”, “C”, “D”, and “X” are based on animal data, limited registry information, and case series/reports. These labels are often confusing and do not fully disclose the risks and benefits of drug exposure during pre-conceptual planning, pregnancy, and lactation. The idea that drug safety in pregnancy is a continuum from X to A is not correct; these categories generally relate to the presence or absence of human or animal data. Notably, 90% of pregnant women take 1 or more prescription medicines and about half take at least 4 medications during pregnancy. The FDA understands the urgency to provide consumers and prescribers with usable information and is committed to work on updating the labels and to improve communication of risk. Furthermore, under the FDA Amendments Act of 2007, the FDA now is requiring pharmaceutical companies to conduct post-marketing trials on pregnant and lactating women and formulate risk evaluation and management strategies (REMS). The NIH and NICHD are interested in collaborating and promoting research in pregnant women and children with autoimmune diseases in basic, translational and clinical research, focusing on drug pharmacokinetics (PK),

Demyelinating Complications Associated with Rituximab and Other Non-Tumor Necrosis Factor-α Inhibitor Biologics

Antonia Valenzuela, MD and Lorinda Chung, MD

Non-Tumor Necrosis Factor (TNF)-α-inhibitor biologics, including rituximab, anakinra, abatacept, and tocilizumab are treatment options for patients with rheumatoid arthritis (RA) when one or more TNF-inhibitors have failed. Although less common than with TNF-inhibitors, demyelinating complications have been associated with some of these medications. Herein we will focus on the demyelinating complications reported with rituximab therapy, and provide a table summarizing the available data for other non-TNF-α-inhibitor biologics (Table).

Rituximab, a chimeric anti-CD20 antibody that promotes cell-mediated and complement-mediated cytotoxicity, inhibits early B cell activation and differentiation, resulting in B cell depletion. The two demyelinating complications reported with rituximab are progressive multifocal leukoencephalopathy (PML) and Guillain-Barre syndrome (GBS). Interestingly, rituximab has been evaluated as a therapeutic option in multiple sclerosis, neuromyelitis optica spectrum disorders, and chronic inflammatory demyelinating polyneuropathy. PML is a serious opportunistic infection caused by reactivation of the JC virus. PML is characterized by progressive inflammation and demyelination of the white matter of the brain, and commonly presents with altered mental status, motor deficits, gait ataxia, and visual symptoms. Rituximab has been

see ACR Reproductive Health Summit on the Management of Pregnant and Lactating Women with Autoimmune Diseases, page 2

see Demyelinating Complications Associated with Rituximab and Other Non-Tumor Necrosis Factor-α Inhibitor Biologics, page 3
ACR Reproductive Health Summit on the Management of Pregnant and Lactating Women with Autoimmune Diseases  continued from cover

pharmacodynamics (PD), and pharmacogenomics. Dr. Christina Chambers from the OTIS Mother-to-Baby registry spoke of the OTIS experience in tracking pregnant patients with autoimmune diseases with the hope of revealing the effects of certain rheumatologic medications and vaccines on pregnancy loss, malformations or early childhood functional deficits. Unfortunately, recruitment numbers and diversity of samples pose a challenge for OTIS. Dr. Jeffrey Curtis also offered his views on strengths and weaknesses of registry data in assessing risks of drugs during pregnancy. He noted that in studying pregnancy, registries are effective in that they are flexible in capturing data and have greater internal validity than spontaneous FDA adverse event reporting. However, there are threats to the validity of registry data owing to confounding factors (e.g., channeling bias, disease severity, sample sizes, comorbidities). Often, there is no denominator for comparison. Most data collected are voluntary and based on recall.

Next, Drs. Mahmoud Ahmed and Lisa Sammaritano, basic science and clinical research experts in placental and lactation physiology and drug transport, summarized their own and existing data. The placenta is a functional barrier that changes during pregnancy. The permeability of compounds is differentially regulated during each trimester, hence, it cannot be assumed that only compounds of a certain molecular weight or structure can cross the placenta. Each drug must be studied independently, and rodent models are not adequate for safety labeling. Likewise, many variables exist with lactation that would influence drug level in infant blood. These include: transfer rate of drug to breast milk, age of infant, variability in absorption, and genetic differences of infants. Highly protein bound drugs are unlikely to cross into breast milk, and drugs that are found in breast milk may not be detectable in infants’ blood. As most milk is produced prior to nursing, the timing of nursing is important as to how much dose of drug is delivered to the infant. For example, with prednisone, less than 10% of the dose is excreted in breast milk. Peak levels of prednisone in milk occur 2 hours after the dose; it is recommended that breastfeeding occurs 4 hours after any dose > 20 mg/day, and infants whose mothers take more than 40 mg/day of prednisone should be monitored for steroid effects. Drugs generally considered safe in breastfeeding include: hydroxychloroquine, sulfasalazine, tacrolimus, warfarin, heparin, and IVIG. Although insufficient data exist for azathioprine, the World Health Organization and American Academy of Pediatrics recommend against breastfeeding while taking azathioprine due to theoretical concerns for bone marrow suppression, susceptibility for infection, and pancreatitis; however, one study published results of 8 infants of women on azathioprine bid who were breastfeeding and had undetectable drug metabolites in their blood (11). Medication use where mothers should avoid breastfeeding include: methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide (these too are based on theoretical risks, rather than data). Although small amounts of IgG1 are secreted in breast milk, tumor necrosis factor inhibitors (TNFi) are generally thought to be safe in breastfeeding as the infant’s digestive tract will break down the protein. Currently, no data is available regarding the safety of rituximab or tocilizumab in lactation.

Drs. Uma Mahadevan, Megan Closowe, and Eliza Chakravarty presented data on different disease states (inflammatory bowel disease [IBD], rheumatoid arthritis [RA], and systemic lupus erythematosus [SLE], respectively) and their effects on pregnancy. The one message that was consistent across all disease states was: Uncontrolled inflammation adversely affecting the mother will create a hostile environment for the fetus. Dr. Mahadevan noted that while TNFi are generally considered safe in pregnancy, clinicians should consider stopping infliximab and adalimumab in the 3rd trimester as 80% of immunoglobulins (including IgG bound biologics) cross the placenta at this time. The concern is that giving live vaccines such as BCG to these infants may cause disseminated disease as has been reported in a case where the mother was receiving infliximab 10 mg/kg every 8 weeks, and the baby died of disseminated BCG (2). Dr. Clossow noted that while RA is expected to improve in pregnancy, disease activity may persist and flares do occur. Patients who have higher disease activity are at increased risk for preterm labor and deliver babies with smaller birth weights. Treating flares with prednisone may not be the optimal approach as the drug may increase risk for infection, preeclampsia, and preterm labor. TNFi are frequently used in IBD patients prior to and during pregnancy as patients are highly prone to flares and complications (especially ulcerative colitis patients) when TNFi or thiopurines are withdrawn. Thus far, the IBD experience has shown no increased risk for malformations with TNFi use, and the same can be said for RA patients exposed to TNFi during pregnancy. In the event that patients suspend TNFi therapy, Dr. Clossow suggested restarting drug 1-2 weeks post-partum to reduce the risk for postpartum flares. In SLE, pregnancy morbidity is a recognized complication as cited by Dr. Chakravarty. Risks for pregnancy loss, preterm labor, and maternal adverse events are significantly higher in patients who have active disease at the onset of pregnancy. In addition, distinguishing preeclampsia from active lupus nephritis is often difficult as there are no good biomarkers to differentiate the two. Studies have shown that hydroxychloroquine improves pregnancy outcomes and that azathioprine and cyclosporine can be safely administered during pregnancy (3). Rituximab, cyclophosphamide, and IVIG have been used safely in life threatening or organ threatening disease in established pregnancy. Despite improved management of lupus pregnancies, there are still more questions than answers. Methotrexate and mycophenolate mofetil (commonly used in SLE) are thus not recommended during pregnancy.

The meeting concluded with final remarks from Dr. Gideon Koren, a leading pediatrician, pharmacologist, toxicologist and founder of Toronto’s MOTHERISK program (www.motherisk.org). He emphasized that there are less than 30 drugs on the market that are known teratogens and only one (Accutane) that carries the same magnitude of teratogenic risk as thalidomide. He stated the only clear teratogens used in rheumatology are methotrexate and mycophenolate. Leflunomide (a category X drug) is “probably not” a teratogen as there is a small OTIS study of 45 leflunomide-exposed RA patients that showed no untoward outcomes (3). Nevertheless, patients will often assign high teratogenic risk to a drug even when the drug is non-teratogenic. He noted that it is necessary to disseminate good information to avoid unnecessary pregnancy termination.

Currently, an unfortunate communication chasm exists between those managing pregnant and lactating women (e.g., obstetricians/gynecologists, maternal fetal medicine, pediatricians, family practitioners) and those who manage their complex and chronic autoimmune diseases (e.g., rheumatologists, gastroenterologists, dermatologists). The goal of the Reproductive Health Summit was to identify what is known and what is remaining unanswered with regard to managing patients with autoimmune diseases antenatally and postnatally. The full proceedings of the Reproductive Health Summit will be published in the near future with the hope of improving communications and pregnancy management across all specialties. D S Q

References


Demyelinating Complications Associated with Rituximab and Other Non-Tumor Necrosis Factor-α Inhibitor Biologics  continued from page 1

Associated with more than 60 cases of PML,10 including 14 in the setting of rheumatic diseases, with an estimated cumulative risk of 5/100000 exposed RA patients. Molloy et al9 reviewed all cases of PML and JC infection within the Food and Drug Administration Adverse Event Reporting System database from November 1997 to March 2010 and identified 34 cases of PML associated with rheumatic diseases. Rituximab was the most recent biologic agent in 14 cases of PML confirmed by detection of JC virus DNA in the cerebrospinal fluid or brain biopsy specimen. PML developed after a median of 2 courses of rituximab and a median time interval of 12 months after the first infusion, resulting in death of 5 patients. Of note, PML was not reported in association with the use of tocilizumab or abatacept although belatacept, a biologic with structural similarities to abatacept has been linked to PML. Determining the risk of PML with rituximab is confounded by the concomitant use of other immunosuppressive drugs and the unclear incidence of PML in rheumatic diseases in the absence of therapy.2

Anecdotal observations of the development of GBS have been reported in immunocompromised patients with hematologic diseases who have been treated with rituximab.11-13 Jaso et al11 reported a case of GBS in an 86-years-old man with B-cell Non-Hodgkin lymphoma (NHL) treated with combined CHOP (cyclophosphamide, doxorubicin, vincristine, and methylprednisolone) and rituximab (375 mg/m²) therapy every two weeks. After the third course, the patient complained of mild paresthesia at the fingertips. He was subsequently diagnosed with GBS and treated with IVIG with complete recovery over 2 months.

Although the causal relationship in the pathogenesis of demyelinating disorders remains uncertain, and these are rare adverse events, the devastating nature of PML mandates physicians who prescribe non-TNF-inhibitor biologics, especially rituximab, to be aware of the potential for the development of PML.5-8 Other demyelinating complications have rarely been reported, but physicians should be vigilant for the development of new neurologic symptoms and signs when patients are taking these agents. D.S.Q.

References


Table 1: Summary table

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The FDA is advising consumers not to. May Arthritis and Rheumatism pose a safety risk for those undergoing MR imaging. There is also a concern that iron, if present in these reddish particulates will October 2013. Smaller pieces of the particulate may pass through the catheter Lidocaine HCl Injection 2%, 5mL distributed between September 2013 and Red particulates in lidocaine vials. Arth-Q is labeled in English, but is also promoted to the Korean-speaking community. when consumers may already be using NSAID-containing products. Arth-Q contains ibuprofen. This hidden drug ingredient may interact with other medications and significantly increase the risk of adverse events, particularly for joint, muscle and arthritic pain since FDA laboratory analysis revealed that any potential benefit accrued by lifting the warning for one (Naproxen) or continued from page 3. FDA MEDWATCH: Spring 2014 NSAIDS are indistinguishable from each other with respect to cardiovascular risks. In its advisory meeting on February 10 and 11th, 2014, the arthritis advisory committee and drug safety and risk management advisory committees voted 16 to 9 to continue the cardiovascular risk warning label for NSAIDS. This discussion was prompted by a recent systematic review performed by Oxford University researchers who reviewed results from more than 700 NSAID studies involving roughly 350,000 patients. The committee carefully reviewed the data on risk differences between various NSAIDs and ruled that any potential benefit accrued by lifting the warning for one (Naproxen) or more NSAIDs will be offset by the risks associated with NSAIDS. Since 2005 all NSAIDS (including over the counter products) include labels that warn the users about the potential adverse cardiovascular outcomes. A second vote, promoted by a Dutch study that indicated that the adverse risk of NSAIDS become apparent as early as a few days and that chronic use is not necessary, assessed the need for updating the package label warning. A majority 14 to 11 voted to recommend revising the package labels incorporating the short term risk warnings. Ibuprofen in dietary supplement. The FDA is advising consumers not to purchase or use Arth-Q, a product promoted and sold as a dietary supplement for joint, muscle and arthritic pain since FDA laboratory analysis revealed that Arth-Q contains ibuprofen. This hidden drug ingredient may interact with other medications and significantly increase the risk of adverse events, particularly when consumers may already be using NSAID-containing products. Arth-Q is labeled in English, but is also promoted to the Korean-speaking community. Low dose diclofenac for osteoarthritis. The FDA has accepted for review the supplemental New Drug Application (sNDA) for Zorvolex (diclofenac), a lower dose nonsteroidal anti-inflammatory drug for the treatment of osteoarthritis pain in adults. This sNDA application is based on data from a 12-week, multi-center, randomized, double-blind, parallel-group, placebo-controlled trial that enrolled 305 patients, aged 41-90 years, with osteoarthritis of the hip or knee. Participants were randomized to Zorvolex 35mg three times daily or 35mg twice daily, or placebo. The sNDA also included data from a 12-month open-label study that enrolled more than 600 patients. Zorvolex was developed to address the FDA’s public health advisory recommending that NSAIDS be used at the lowest effective dose for the shortest duration consistent with individual patient treatment goals. The manufacturer states that the advantages of this preparation of diclofenac include about 23% less systemic exposure to diclofenac and avoidance and sodium and potassium in the preparations. Zorvolex is already approved for the treatment of mild to moderate acute pain in adults. The retail price of this proprietary product is expected to be substantially high (>$150 per month) compared to generic diclofenac of any strength. Tightening the prescription guidelines for acetaminophen. Based on emerging evidence suggesting that doses greater than 325 mg acetaminophen per dosing unit do not have any additional benefit to the patient, and some suggestion that it increases the risk for overdose, the FDA no longer wants higher strength acetaminophen to be used. This is not a new move. Limiting the amount of acetaminophen in combination products has been on the FDA’s agenda since its initial communication with manufacturers back in January 2011 when they were asked to cease production of high-strength acetaminophen. While some products with higher doses still remain on the market, pharmacists who receive prescriptions for products containing more than 325 mg of acetaminophen per dosage unit should contact the prescriber to discuss products that contain a lower dose. Higher doses (such as 650 mg) are still permitted as long as multiple capsules/tablets of the lower strength are dispensed.
FDA MEDWATCH: Spring 2014 continued from page 4

Generic versions of Cymbalta™ approved. The FDA has provided approvals to 6 manufacturers for marketing generic duloxetine in the United States.

Abuse-deterrent opioid analgesics. The FDA is expected to rule on a New Drug Application (NDA) for Targiniq ER (oxycodone HCl/naloxone HCl controlled-release) for the management of chronic pain. The NDA submission was based on the results of a 12-week, double-blind, randomized, placebo-controlled clinical trial with 800 opioid-experienced patients as well as supporting data from other clinical studies. The submission also includes data from clinical abuse liability studies designed and conducted as per FDA’s January 2013 Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling. If approved by the FDA, Targiniq ER will be available in 10/5 mg, 20/10 mg and 40/20 mg dosage strengths.

Generic version of Lidoderm™. Actavis® announced the launch of Lidocaine Topical Patch 5%, the generic version of Endo Pharmaceutical’s Lidoderm indicated for postherpetic neuralgia. The manufacturer has indicated that the medication is now available in pharmacies.

Safety Signals: March 2014


Aminopterin embryopathy. Low-dose methotrexate in pregnancy is associated with aminopterin embryopathy. The mother, however, was exposed to methotrexate 7.5 mg orally until 10th week of gestation as well as fluconazole (150 mg orally weekly) and rofecoxib (25 mg a day) during the first trimester of pregnancy; and meprednisone (8 mg a day), ranitidine (300 mg daily) and isoniazid (150 mg orally weekly) and rofecoxib (25 mg a day) during the first trimester of pregnancy; and meprednisone (8 mg a day), ranitidine (300 mg daily) and isoniazid (300 mg daily) throughout pregnancy. Martin MC, Barbero P, Groisman B, Aguirre MA, Koren G. Methotrexate Embryopathy After Exposure to Low Weekly Doses in Early Pregnancy. Reprod Toxicol. 2013 Oct 26. pii: S0890-6238(13)00360-2. doi: 10.1016/j.reprotox.2013.10.005. [Epub ahead of print] PubMed PMID: 24513926.

Spontaneous abortion rates and methotrexate use. Use of methotrexate for autoimmune rheumatic disease in general was associated with pregnancy loss of about 42% of reported cases. The risk for birth defects were almost twice as high among the babies compared to the babies born to women not using methotrexate. However, use of methotrexate prior to conception was not statistically associated with any such risk elevations. Weber-Schoendorfer et. al. C. Pregnancy outcome after rheumatologic methotrexate (MTX) treatment prior to or during early pregnancy: A prospective multicenter cohort study. Arthritis Rheumatology. 2014 Jan 27. doi: 10.1002/art.38368. [Epub ahead of print] PMID: 24470106.