Managing Rheumatologic Diseases in Pregnancy

BY BRUCE JANCIN

SNOWMASS, COLO. — Corticosteroids can be thought of as the "go-to" drugs for the management of rheumatologic disorders in pregnancy.

"Corticosteroids have been my ace in the hole in treating many patients during pregnancy. They're potent immunosuppressives that can get you out of a lot of trouble. And although they can have side effects, if used judiciously they are a reasonable treatment choice," Dr. Bonnie L. Bermas stressed at a symposium sponsored by the American College of Rheumatology.

Transplant registries comprising tens of thousands of organ recipients have shown no increased rate of congenital anomalies with the use of corticosteroids in pregnancy. However, an influential University of Toronto meta-analysis concluded that "although prednisone does not represent a major teratogenic risk in humans at therapeutic doses, it does increase by an order of 3.4-fold the risk of oral cleft" (Teratology 2000;62:385-92).

"What this translates to in your practice is, the cleft palate incidence increases from 1 in 1,000 in the general population to about 1 in 300 live births exposed to steroids in utero. That's how I counsel my patients who need to be on corticosteroids in the first trimester," said Dr. Bermas, clinical director of the lupus center at Brigham and Women's Hospital in Boston.

After 12-14 weeks' gestation, the palate is formed; steroids are no longer associated with an increased risk for cleft palate after that point. But other risks remain, including gestational diabetes, gestational hypertension, osteoporosis in the mother, premature rupture of the membranes, and small-for-gestational-age infants. Prednisone and methylprednisolone—the steroids rheumatologists utilize most often—don't cross the placenta efficiently, and are much less likely to cause fetal adverse effects than are dexamethasone or betamethasone.

Corticosteroids are potent and 'can get you out of a lot of trouble,' even with their side effects.

DR. BERMAS

Steroids that are administered to the mother make their way into breast milk only in low concentrations. If she's on less than 20 mg/day of prednisone, she can breastfeed normally. For women on higher doses, Dr. Bermas advises pumping and discarding the breast milk for the first 4 hours after a dose is taken.

The key to successful treatment of rheumatologic disorders during pregnancy is a clear assessment of the patient's tolerance for risk—and the physician's, as well, Dr. Bermas said. "There are some women who do not drink caffeinated beverages or take any medications, not even a Tylenol, and who will eat only organic foods while pregnant. . . . And as clinicians, we have our own risk tolerances, too. For example, azathioprine is a medication that I feel comfortable using during pregnancy, but I have colleagues who won't because they wouldn't be able to sleep at night," she said.

The reason she prescribes azathioprine during pregnancy—despite its category D rating from the Food and Drug Administration, indicating "positive evidence of risk"—is that there's an enormous transplant literature showing no increase in congenital anomalies with in utero exposure to this drug. Mycophenolate mofetil (CellCept) also has a category D rating. But unlike azathioprine, it has no extensive and reassuring transplant literature, so Dr. Bermas said she avoids it in pregnant and nursing patients.

Other rheumatologic medications to avoid in pregnancy are methotrexate, penicillamine, 6-mercaptopurine, and chlorambucil, she continued.

The use of tumor necrosis factor inhibitors during pregnancy is an extremely challenging question. Although at present the FDA rates them as category B ("no evidence of risk in humans"), that could very well change as a result of a reported association (J. Rheumatol. 2009;36:635-41) with VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, and limb) anomalies.

When lupus patients on antimalarials become pregnant, Dr. Bermas said she generally keeps them on the medication. She also allows patients to remain on antimalarials while nursing, which is consistent with the position of the American Academy of Pediatrics.

For mild cases of rheumatologic disease in pregnancy, Dr. Bermas said that she relies on NSAIDs and/or prednisone at 5-10 mg/day. She halts the NSAID after the second trimester in order to avoid premature closure of a patent ductus arteriosus. For an inflammatory mild arthritis, she considers adding sulfasalazine.

She manages moderate disease with higher-dose steroids, azathioprine, or cyclosporine. For severe disease, Dr. Bermas reported that she turns to pulse steroids, azathioprine, cyclosporine, or intravenous immunoglobulin. In life-or-death situations, there are many case reports of cyclophosphamide being used successfully in the third trimester, a time by which most organogenesis is completed. ■

Disclosures: *Dr. Bermas reported having no financial conflicts of interest.*

Screening Key to Managing Hepatic Risks in Rheumatology

BY BRUCE JANCIN

SNOWMASS, COLO. — Screening for both hepatitis C and B is a reasonable strategy in all patients who are under consideration for any disease-modifying antirheumatic drug. "If they turn out to be infected, you've done them a huge favor. Send them to a hepatologist for treatment," advised Dr. Leonard H. Calabrese.

And just because they have chronic viral hepatitis doesn't mean that their comorbid rheumatic disease can't be aggressively treated, provided they don't have decompensated liver disease and are Child-Pugh class A, he stressed at a symposium sponsored by the American College of Rheumatology.

Evidence suggests that in chronic HCV, anti–tumor necrosis factor (anti-TNF) therapy not only is safe, it actually may also substantially improve the tolerability of antiviral therapy with interferon and ribavirin, thereby boosting the hepatitis cure rate, said Dr. Calabrese.

This possibility was first broached a half-decade ago in a positive double-blind, placebo-controlled, phase II study of etanercept (Enbrel) (J. Hepatol. 2005;42:315-22). The manufacturer resisted hepatologists' subsequent pleas to mount a definitive clinical trial. However, such a study is now underway using another anti-TNF drug, infliximab (Remicade).

The 52-week, multicenter, blinded, randomized PARTNER (Pegylated Interferon Ribavirin and Anti-TNF Enhanced Response) trial, sponsored by the Cleveland Clinic, has completed just over half of its enrollment. Eligibility is restricted to patients with chronic HCV with genotype 1, the most treatment-resistant form of the disease. These patients don't have concomitant rheumatic disease; they are being randomized to anti-TNF therapy solely in an effort to improve the results of their antiviral regimen.

However, several reports published in the literature point to the safety of anti-TNF therapy in patients with chronic HCV and comorbid rheumatic diseases. Dr. Calabrese highlighted what he termed a "thoughtful and reassuring" seven-center prospective Italian series involving 31 chronic HCV-infected patients with rheumatoid arthritis (RA) refractory to nonbiologic disease-modifying antirheumatic drugs (DMARDs). After a mean 22 months of treatment with infliximab, etanercept, or adalimumab, the patients showed marked lessening of their rheumatic disease with no adverse effects on liver enzymes or HCV viral load (J. Rheumatol. 2008;35:1944-9).

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DR. CALABRESE

Based upon such favorable reports as well as the results of the earlier etanercept study, Dr. Calabrese reported that he turns to anti-TNF biologic agents as first-line therapy in HCV-infected patients who require remittive therapy for a rheumatic disease. He makes sure they have a baseline liver biopsy, carefully monitors their liver enzymes, and considers rebiopsy at 3-5 years.

"At this point in time, there are more data on the safety of biologics than nonbiologic DMARDs in the setting of HCV," according to Dr. Calabrese, professor of medicine at the Cleveland Clinic Foundation.

The use of DMARDs in patients with chronic HBV is a considerably more complex issue. That's because there is evidence that any form of immunosuppressive therapy—biologics, older DMARDs, or moderate- or high-dose systemic corticosteroids—can trigger a severe or even fatal flare of hepatitis B if the therapy is interrupted or discontinued.

Nonetheless, there are multiple reports of HBV-infected patients who are being successfully treated for rheumatoid arthritis and other rheumatic diseases with biologic agents or conventional DMARDs, provided they are started on prophylactic antiviral therapy beforehand. For example, Italian investigators reported no cases of HBV reactivation in 20 patients with rheumatic diseases who were treated with biologic DMARDs during a median 19 months of prophylactic antiviral therapy with lamivudine at 100 mg/day (Reumatismo 2008;60:22-7).

Today, there are much better antivirals than lamivudine for this purpose, Dr. Calabrese pointed out. Nucleotide analog reverse transcriptase inhibitors such as adefovir (Preveon) and tenofovir (Viread) are very easy to use and have far fewer resistance issues. The experience to date strongly suggests that the newer agents can be given for the patient's full remaining life span.

There are at present no consensus guidelines in rheumatology that address screening for HCV and HBV. Dr. Calabrese advocated screening liberally; these are two of the biggest public health problems of the era, and treatment has progressed rapidly. He believes that all candidates for DMARD therapy ought to be screened, as well as any rheumatology patient who is at high risk for HCV or HBV. "HBsAg is what you're really looking for. If you're positive, you're a carrier, and you're infected," he said. ■

Disclosures: *Dr. Calabrese disclosed serving as a paid consultant to Genentech Inc., Roche, Amgen Inc., Centocor Inc., UCB Pharma Inc., Sanofi-Aventis, and Wyeth.*