

Managing Rheumatologic Diseases in Pregnancy

BY BRUCE JANCIN

FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

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 the symposium.

Reassuringly, transplant registries comprising many 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 has concluded that “although prednisone does not rep-



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DR. BERMAS

resent 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, however, the palate is formed. And although steroids are no longer associated with an increased risk for cleft palate after that point in gestation, other risks remain. These include 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 hence are much less likely to cause fetal adverse effects than are dexamethasone or betamethasone.

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.

Dr. Bermas emphasized that the key to successful treatment of rheumatologic disorders during pregnancy is a clear-

eyed assessment of and accommodation to the patient’s tolerance for risk—and the physician’s, as well.

“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. There are others who are willing to tolerate some risk during pregnancy. 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 explained.

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, mycophenolate mofetil has no extensive and reassuring transplant literature. As a result, Dr. Bermas said that she avoids it in pregnancy and nursing.

Other rheumatologic medications to avoid in pregnancy are methotrexate, penicillamine, 6-mercaptopurine, and



Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

INDICATION

Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia™ reduces the incidence of vertebral, nonvertebral, and hip fractures.

IMPORTANT SAFETY INFORMATION

- ♥ **Hypocalcemia:** Prolia™ is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia™. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.
- ♥ **Serious Infections:** In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia™ group than in the placebo group. Serious skin infections, as well as infections of

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia™. Endocarditis was also reported more frequently in Prolia™-treated subjects. The incidence of opportunistic infections was balanced and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia™, prescribers should assess the need for continued Prolia™ therapy.

- ♥ **Dermatologic Adverse Reactions:** Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia™ group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Prolia™ if severe symptoms develop.

- ♥ **Osteonecrosis of the Jaw (ONJ):** ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia™. An oral exam should

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 anomalies, which include vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities. On the other hand, several editorials and review articles have expressed the view

that the risk of VACTERL anomaly after in utero exposure is overstated.

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

Academy of Pediatrics.

For mild cases of rheumatologic disease in pregnancy, Dr. Bermas reported 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 said 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.

Dr. Bermas reported having no financial conflicts of interest. ■

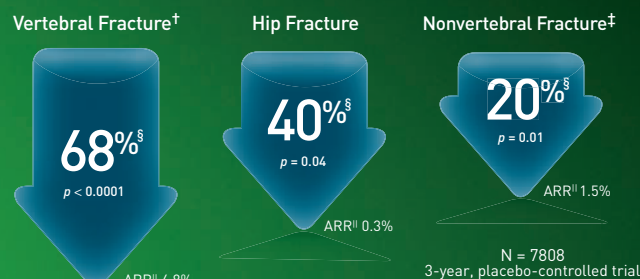
'Azathioprine is a medication that I feel comfortable using during pregnancy, but I have colleagues who won't because they wouldn't be able to sleep at night.'

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Please see Brief Summary of Prescribing Information on the following page.

be performed by the prescriber prior to initiation of Prolia™. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia™.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia™ should be considered based on individual benefit-risk assessment.

Suppression of Bone Turnover: Prolia™ resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions: The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia™.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia™ groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

Prolia™ Postmarketing Active Safety Surveillance Program: The Prolia™ Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to www.proliasafety.com or call 1-800-772-6436 for more information about this program.

* Key sites: vertebral, hip, and nonvertebral.^{1,2}

† Includes 7393 patients with a baseline and at least one post-baseline radiograph.^{1,2}

‡ Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.^{1,2}

§ RRR = relative risk reduction.

¶ ARR = absolute risk reduction.

References: 1. Prolia™ (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.

For more information, visit www.ProliaHCP.com


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MC48223-C 10-10