Some DMARDs Shown to Lower Diabetes Risk

BY MARY ANN MOON

FROM JAMA

Some disease-modifying antirheumatic drugs that are taken for rheumatoid arthritis or psoriasis appear to reduce the rate of incident diabetes.

In a retrospective cohort study of patients who had RA or psoriasis, the use of a tumor necrosis factor (TNF) inhibitor or hydroxychloroquine to treat the systemic inflammatory disorder was associated with a reduced risk of developing diabetes, compared with the use of methotrexate or nonbiologic DMARDs, said Dr. Daniel H. Solomon of the divisions of phamacoepidemiology and rheumatology at Brigham and Women's Hospital, Boston, and his associates.

"Considering these results, in light of prior findings regarding improved insulin and glucose metabolism and reduced diabetes risk with hydroxychloroquine and TNF inhibitors, there is evidence suggesting a possible role for DMARDs and immunosuppression in diabetes prevention," they noted.

The investigators assessed the relationship between DMARDs and the risk of new-onset diabetes because previous studies have demonstrated that inflammatory conditions such as RA and psoriasis predispose patients to insulin resistance, and that some of these anti-inflammatory medications appear to improve insulin resistance and prevent the onset of diabetes. They analyzed information from the databases of a Canadian health care system and a commercial U.S. health plan to identify 13,905 adults with RA or psoriasis who had filled at least one prescription for a DMARD and could be followed for approximately 6 months.

The DMARDs were divided into four mutually exclusive groups. The four groups were (1) TNF inhibitors such as adalimumab, etanercept, or infliximab; (2) methotrexate; (3) hydroxychloroquine; and (4) other nonbiologic DMARDs such as sulfasalazine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, 6-thioguanine, acitretin, D-penicillamine, and the following gold preparations: auranofin, myochrysine, or solganol.

A total of 267 study subjects developed incident diabetes. The incidence was highest among patients who were taking nonbiologic DMARDs.

Patients taking a TNF inhibitor or hydroxychloroquine showed a reduced risk of diabetes, compared with patients taking any other agents.

After accounting for the effects of potentially confounding factors such as patient age, sex, and several clinical variables, investigators found that the hazard ratios for diabetes were 0.62 for TNF inhibitors and 0.54 for hydroxychloroquine, compared with the nonbiologic DMARDs, Dr. Solomon and his colleagues said (JAMA 2011;305:2525-31).

"These findings held up across a variety of sensitivity analyses," they added.

"Taken in the context of prior research, [our] study supports the potential role for systemic immunosuppression in prevention and control of diabetes.

"If future studies show this convincingly, systemic immunosuppression in such situations would be predicated on a favorable risk-benefit profile."

For example, the benefit of immunosuppression may outweigh the risk in a patient with a systemic rheumatic disease for which a DMARD is already indicated.

But immunosuppression may not outweigh the risk in a patient who already has diabetes and is prone to infection.

The investigators emphasized that this was an observational epidemiologic study without randomized-treatment assignment, so causation cannot be inferred.

"It is possible that patients receiving a TNF inhibitor or hydroxychloroquine were different from the reference group of other nonbiologic DMARD users in ways that went unmeasured, such as body mass index, exercise participation, family history, or disease severity," they noted.

They added that the findings warrant confirmation in a randomized, controlled trial to test "the ability of these agents to prevent diabetes among participants with systemic inflammatory disorders." ■

VITALS

Major Finding: The hazard ratios for diabetes were 0.62 for patients taking TNF inhibitors and 0.54 for patients taking hydroxychloroquine, compared with patients taking nonbiologic DMARDs to treat their rheumatoid arthritis or psoriasis.

Data Source: A retrospective observational study involving 13,905 adults who had either RA or psoriasis, received a DMARD, and were followed for approximately 6 months for the development of diabetes. Participants were enrolled in one of two health care systems.

Disclosures: This study was supported by Amgen. Dr. Solomon reported ties to Abbott, Amgen, Bristol-Myers Squibb, and Pfizer, and his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Confirmation Still Needed

"Prospective trials are needed to confirm [these] observational data and clarify which patients may benefit from these possible pleiotropic effects of specific anti-inflammatories," said Dr. Tim Bongartz and Dr. Yogish C. Kudva.

If TNF inhibitors or hydroxychloroquine prove to address two complex disease processes at once, "it will be crucial to investigate how much of their potential antidiabetic effects would add to good disease control, the durability of these effects, and the timing of treatment."

Even if treatment of chronic inflammatory disease can reduce the risk of diabetes, "clinicians still will have to learn how to use specific anti-inflammatory agents to achieve optimal outcomes for both conditions," they said.

DR. BONGARTZ is in the division of rheumatology and DR. KUDVA is in the division of endocrinology, diabetes, metabolism, and nutrition at the Mayo Clinic in Rochester, Minn. Dr. Bongartz reported ties to Wyeth and Abbott. Dr. Kudva reported no conflicts of interest. These remarks were taken from their editorial accompanying Dr. Solomon's report (JAMA 2011;305:2573-4).

DRUGS, PREGNANCY, AND LACTATION

Drugs Approved in 2010

In 2010, the Food and Drug Administration approved 21 new chemical entities, 3 of which have human pregnancy data. Of these three, one is used in rheumatology: Actemra (pregnancy risk category C). Pregnancy data are unavailable for the other rheumatologic drug in the group, the anti-gout drug pegloticase.

BY GERALD G. BRIGGS, B.PHARM., FCCP

It is best to avoid prescribing new drugs for women of childbearing potential or during pregnancy, and to use older agents with human pregnancy experience. But what if the new drug is a major breakthrough or is the only or most efficacious drug to treat your patient's condition? How do you counsel the patient about a drug's risk to her embryo or fetus when there is little or no human pregnancy data? Fortunately, the package insert provides data for three of the four factors that can be used to give some estimate of risk: drug class, potential to cross the placenta, and animal data. Then, when your patient asks "What are the risks?" you don't have to say "We just don't know."

The antigout agent pegloticase (Krystexxa; C), a pegylated uric acid specific enzyme, is given as an intravenous infusion every 2 weeks. The high molecular weight should prevent the enzyme from crossing the placenta.

Among the drugs approved in 2010 are two immunologic agents, both of which are monoclonal antibodies. These are denosumab (Prolia; C), indicated for postmenopausal women with osteoporosis, and tocilizumab (Actemra; C), indicated for rheumatoid arthritis. Denosumab will probably cross the placenta in the third trimester and should not be used in pregnancy. Tocilizumab caused abortion and embryo death in monkeys. The known pregnancy outcomes in 31 patients exposed to the drug were 7 spontaneous abortions, 13 elective abortions, 10 healthy term newborns, and 1 neonatal death of a term infant at 3 days of age. One reference recommends stopping tocilizumab 3 months before conception (Curr. Opin. Rheumatol. 2011; 23:293-8).

Collagenase clostridium histolyticum (Xiaflex; B) is given intramuscularly for the treatment of Dupuytren's contracture with a palpable cord. Because it has not been detected in the systemic circulation, it poses no direct risk to a pregnancy. However, all patients develop antibodies against the drug and the effect of the antibodies on the embryo-fetus is unknown.

These drugs appear to be compatible with breastfeeding, but infants should be closely monitored for signs and symptoms of toxicities commonly seen in adults. ■

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