Tuberculosis Risk Up In Glucocorticoid Users

BY KERRI WACHTER
Senior Writer

Patients taking a glucocorticoid have a nearly fivefold increased risk of developing tuberculosis, independent of other risk factors.

"Our results suggest that glucocorticoid use is associated with a substantially increased risk of developing tuberculosis and that the risk increases with increasing daily dose," said Susan S. Jick, Sc.D., of Boston University, and her colleagues.

Although chronic corticosteroid use is common in patients with rheumatic diseases, the number of such patients in the study population was too small to say definitely if use of corticosteroids specifically for arthritis and other rheumatic diseases was associated with an increased risk for TB.

Patients who were currently on corticosteroids were 4.9 times more likely to get tuberculosis than nonusers, even after adjustment for confounding factors.

Low body mass index (BMI), diabetes, current smoking, and obstructive pulmonary disorders were also determined to be important risk factors for tuberculosis in a review of 497 new cases of tuberculosis and 1,966 matched controls during the period 1990-2001 (Arthritis Rheum. 2006;55:19-26).

The researchers based their study on data available from the U.K.-based General Practice Research Database. Started in 1987, the validated computerized medical record system includes more than 3 million people enrolled with selected general practitioners. Participants had a first-time diagnosis of tuberculosis followed by treatment with at least three different antituberculosis medications for at least 6 months.

As many as four control subjects were matched to each patient based on age, gender, practice attended, and the patient's index date, along with time of visit.

Assessment of glucocorticoid use was based on prescription data. Patients were classified as currently exposed if they had received a prescription for any oral glucocorticoid and if the supply had lasted until within 120 days prior to the index date. Recent exposure was defined as use ending 121-180 days before the index date. All other use more than 180 days prior was considered past use.

The researchers also assessed current exposure to antirheumatic drugs or immunosuppressants and the presence of pulmonary disorders, rheumatic disorders, inflammatory bowel diseases, dermatitis, silicosis, renal failure, gastrectomy, and jejunoileal bypass surgery (diagnosed prior to the index date).

Patients currently using corticosteroids were 4.9 times more likely to develop tuberculosis than nonusers, even after adjustment for BMI, smoking, disease-modifying antirheumatic drug use, and history of diabetes and pulmonary disease. The risk for tuberculosis remained higher (OR 4.3) in patients who had recently stopped using corticosteroids.

First-time users were 3.2 times more likely to get tuberculosis than were never users. Patients with longer-term use, extending over two to nine consecutive prescriptions, saw their risk increase sevenfold.

The effect of corticosteroid use on risk for TB increased with increasing dose. The OR was 2.3 in people taking daily doses of prednisone equivalents less than 7.5 mg daily (physiologic) versus those taking supraphysiologic doses of 7.5 mg or more daily (OR 7.0, based on the highest daily dosage received by current users).

Both the American Thoracic Society and the Centers for Disease Control and Prevention agree that more than 15 mg/day of prednisone or its equivalent administered for 1 month or longer is a risk factor for tuberculosis. In light of this, the researchers evaluated the impact of daily dosage using this cutoff. The adjusted odds ratio was 2.8 for those using less than 15 mg of prednisone equivalents per day; those using 15 mg of prednisone equivalents per day or more had an adjusted odds ratio of 7.7.

We found that current smoking was associated with a 60% increased risk of tuberculosis. Although this effect is relatively low, because smoking is prevalent in this study population, 17% of all cases are attributable to smoking, compared with only 8% of cases attributable to glucocorticoid use in this population," the researchers said. The odds ratio for past smokers was not significant.

Those with a BMI less than 20 kg/m^2 also had an elevated risk (OR 2.8), while those with a BMI greater than 25 had an odds ratio of 0.5, compared with patients with a BMI of 20-25.

A diagnosis of rheumatic disease and use of antirheumatic agents are purported to be risk factors for tuberculosis as well.

However, the number of patients taking antirheumatic drugs in this analysis was low; only 12 patients were currently exposed. Overall, 17 participants (cases and controls) had rheumatoid arthritis, 1 had lupus, 12 had polymyalgia rheumatica, and 7 had arteritis. "Despite the large number of tuberculosis cases in this study, the prevalence of antirheumatic agent use was low," and thus independent effects for patients on antirheumatics could not be assessed reliably, the researchers noted. ■

ProQuad Suitable to Replace Second-Dose MMR or MMRV

BY HEIDI SPLETE
Senior Writer

A combination MMR-varicella vaccine can be substituted for the second dose of the MMR vaccine or for the second doses of coadministered MMR and varicella vaccines in children aged 4-6 years, reported Dr. Keith S. Reisinger of Primary Physicians Research in Pittsburgh, and his associates.

Dr. Reisinger and his colleagues found postvaccination seropositivity rates of nearly 100% for the combination measles, mumps, rubella, and varicella vaccine (ProQuad) in a randomized, double-blind multicenter study sponsored by Merck & Co., including 799 healthy children (Pediatrics 2006;117:265-72).

Dr. Reisinger serves as a speaker for Merck and receives research money from the company.

The children had received their primary doses of the measles, mumps, and rubella vaccine (Merck-brand MMRII vaccine) and the varicella vaccine (Varivax) at age 12 months or older at least 1 month before their enrollment in the study.

A total of 399 children received ProQuad as a single injection, plus a placebo, while 205 children received the standard MMRII plus a placebo, and 195 received MMRII plus Varivax. About half the children (53%) were male, most (79%) were white, and their mean age was 4 years.

Overall, the immune responses to all four viruses, as measured by geometric mean titers (GMTs), in children who received ProQuad were statistically similar to those in children who received the other vaccines, although there were differences in GMTs with respect to the individual viruses. The GMTs of antibodies to mumps alone were statistically lower in the ProQuad group, compared with the other groups, but the GMTs of antibodies to rubella and varicella in the ProQuad group were higher, compared with the other groups, Dr. Reisinger and his associates wrote.

No severe vaccine-related adverse events were reported, and the percentages of any adverse events were similar among the groups. The most common problems were fever, nasopharyngitis, and cough. There were no significant differences in injection-site adverse experiences in the ProQuad group, compared with the other groups.

The concentration of varicella vaccine virus was higher in the ProQuad vaccine than in the current Varivax varicella vaccine, but the concentrations of measles, mumps, and rubella viruses were the same as those in the current MMRII vaccine.

"The use of [measles, mumps, rubella, and varicella] MMRV will increase varicella protection in a similar fashion that MMR did for lagging mumps and rubella vaccine utilization in the early '70s," Dr. Reisinger said. Secondly, some parents and physicians are concerned about the high number of injections that infants receive in the first 2 years of life. The use of MMRV will be helpful in reducing the number of shots.

"Although the above factors are important, the largest issue to me is the need [for the United States] to move toward a two-dose varicella policy. Every vaccine has a primary failure rate. For MMR this primary failure rate is corrected through the recommendation of two doses.

"If the United States adopts a second varicella dose recommendation (as surely it must), the combined MMRV administered at 4-6 years of age will be the vaccine of choice to accomplish this," he said. ■

Proxy Clinical Markers for Shiga Toxin Load Help Determine Disease Severity

WASHINGTON — The severity of disease caused by Shiga toxin–producing bacteria may be tracked with a new scale under development that uses clinical markers of disease rather than direct measurement of toxin load, Dr. Martin M. Bitzan reported at a biodefense research meeting sponsored by the American Society for Microbiology.

"While the clinical diagnosis of hemolytic uremic syndrome appears straightforward, there are no defined criteria to describe and grade the severity of hemolytic uremic syndrome or of the preceding gastrointestinal disease," Dr. Bitzan of the department of nephrology at Montreal Children's Hospital wrote in a poster presentation.

The inability to measure Shiga toxin in body fluids makes the development of proxy markers necessary, he and his colleague noted. Most of the infections in North America are due to *Escherichia coli* O157:H7.

The investigators developed a disease severity scale comprising four facets of Shiga toxin–producing infections: enteropathy (stool frequency, bloody diarrhea, abdominal pain); inflammation and vasculopathy (fever, peripheral leukocytosis, hypoalbuminemia); thrombotic microangiopathy (low hemoglobin and platelet levels); and nephropathy (hematuria, proteinuria, pyuria, hyponatremia, high serum creatinine).

They tested their scale on a database of 146 consecutive children aged 1-16 years with Shiga toxin–producing *E. coli* who had bloody (85%) or nonbloody (15%) diarrhea that resulted in partial (5%) or complete (13%) hemolytic uremic syndrome (HUS).

The scores of the children with HUS on all the scale's components except enteropathy became significantly worse 3-5 days after disease onset than children without the syndrome. The symptoms of those three components continued to be worse 11-14 days after disease onset, defined as the first day of diarrheal symptoms. Most children visited the ED for the first time 3 days after onset.

The scale is being validated in an international, prospective, observational study for disease follow-up.

—Jeff Evans