Drug Monitor

Flu Shot and Guillain-Barré Syndrome

Since 1976, reports have suggested that influenza vaccination increases the risk of developing Guillain-Barré syndrome (GBS) by as much as eightfold. Researchers from the University of Toronto and Toronto General Hospital, both in Toronto, Canada, who conducted two studies found a slighter, but still significant, risk elevation: 45% in the first seven weeks after vaccination.

This finding was based on a self-matched case series of 1,601 patients who were hospitalized for GBS between April 1993 and March 2004. Of these patients, 269 had been newly diagnosed with GBS within 43 weeks of vaccination during October or November (the peak of the influenza vaccination campaign in Ontario). The resulting risk elevation persisted through sensitivity analyses that varied the timing of the risk interval (weeks two through seven or two through nine) and the control interval (weeks 26 through 43, 32 through 43, 20 through 43, or 18 through 41).

Despite these findings, the second study, a time-series analysis, demonstrated no evidence of seasonality of GBS admissions and no noticeable increase in the incidence of these admissions after the introduction of a mass public influenza vaccination program in 2000. The researchers conclude that, while the potential benefits of vaccination probably outweigh the risks in most cases, clinicians should advise patients of the possibility of GBS. They also advise that any future mass influenza vaccination program (such as for pandemic flu) incorporate active GBS surveillance.

Source: *Arch Intern Med.* 2006;166:2217–2221.

Hypothyroidism with Sunitinib

Sunitinib can be a boon for some patients with gastrointestinal stromal tumors resistant to imatinib treatment. But these patients may need to be watched for thyroid dysfunction, say researchers from Brigham and Women's Hospital, the Dana Farber Cancer Institute, and Harvard Medical School, all in Boston, MA. Prompted by two index cases of primary hypothyroidism with long-term sunitinib treatment, they conducted a prospective, observational, cohort study of patients enrolled in sunitinib phase I or II trials.

Of 42 patients with normal baseline thyroid-stimulating hormone (TSH) levels who received at least three cycles of sunitinib (median duration of treatment, 37 weeks; range, 10 to 167 weeks), 26 had documented abnormal serum TSH concentrations. Seven patients had mild and transient TSH elevations, but 15 developed persistent, primary hypothyroidism. Another four had isolated TSH suppression, though these patients all discontinued the study before undergoing follow-up thyroid function studies.

Hypothyroidism risk increased with the duration of treatment, with an incidence of 18% among patients who took sunitinib for 36 weeks, 29% among those who took the drug for one year, and 90% among those who took the drug for more than 96 weeks. On average, it took 50 weeks of treatment for signs of hypothyroidism to appear. The researchers say this could explain why they found such higher rates of hypothyroidism compared with earlier trials that involved shorter treatment courses.

Based on the study and on the two index cases, the researchers warn that the condition may progress rapidly from mild to profound hypothyroidism. In addition, a low serum TSH concentration and mild symptoms suggesting thyroiditis-induced thyrotoxicosis may precede the onset of hypothyroidism.

They suggest that patients taking sunitinib undergo frequent TSH measurements (every two to three months). An abnormal value should prompt thorough evaluation. Patients who develop overt hypothyroidism should be treated with levothyroxine, and treatment should be considered even for subclinical disease. The good news, say the researchers, is that the hypothyroidism is "easily treated" without sunitinib discontinuation.

Source: *Ann Intern Med.* 2006;145:660–664.

IFN for Renal Cell Cancer: Impact of Dose

According to findings from MD Anderson Cancer Center in Houston, TX, a lower dose of interferon (IFN) given twice daily may be just as effective as an intermediate dose given once a day for patients with metastatic renal cell cancer—with less toxicity and better quality of life (QOL).

In 118 patients with metastatic renal cell cancer randomly assigned to receive IFN 0.5 million U SC twice daily (IFN 1 group) or IFN 5 million U SC once daily (IFN 5 group), both treatments yielded similar response rates. The median progression free survival rates were 3.7 months in the IFN 1 group and 3.4 months in the IFN 5 group, and the median overall survival rates were 25.5 and 17.5 months, respectively.

While both groups had similar baseline QOL scores, by eight weeks, QOL

and depression scores had worsened to a much greater degree in the IFN 5 group compared with the IFN 1 group. In fact, more than twice as many IFN 5 patients scored above the clinical cutoff point for depression after eight weeks of treatment. In addition, there were significantly fewer grade 3 or higher adverse events in the IFN 1 group (25 events versus 53 in the IFN 5 group).

The researchers, who hypothesized that treatment with the lower IFN dose would be superior (not equivalent) to the intermediate dose, caution that their trial was not designed to detect an absence of difference between the doses. Furthermore, they say that their small sample size makes several conclusions possible—including scenarios in which neither IFN dose provides a clinically meaningful benefit, the intermediate dose results in a modest benefit while the low dose is no better than placebo, or the low dose has an advantage that was undetected in this study. Nevertheless, they speculate that, as novel agents targeting the pathways implicated in renal cell cancer become available, there may be an important role for low dose IFN in combination with these agents.

Source: *Cancer.* 2006;107:2254–2261.

New Indication for Trastuzumab

Trastuzumab, a monoclonal antibody approved in 1998 to treat metastatic breast cancer, now has an expanded use: adjuvant treatment, in combination with standard chemotherapy, of node positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2). The drug, marketed by Genentech Inc. (San Francisco, CA) as Herceptin, targets the HER2 protein which, when present in excessive amounts, can speed cancer cell growth and may compromise the efficacy of standard chemotherapy.

Studies conducted by the National Cancer Institute, which included data on nearly 4,000 women, were halted early due to positive results. The addition of trastuzumab to the chemotherapy regimen significantly reduced the risk of cancer recurrence, second cancers, or death (hazard ratio, 0.48); increased disease free survival rates by 12% at three years; and reduced the risk of death by 33%.

Because trastuzumab has been associated with left ventricular cardiac dysfunction, the drug should be reserved for patients who screen negative for cardiomyopathy, and patients receiving treatment should have periodic heart function monitoring. Other serious adverse events that have been reported, though less frequently, are severe infusion reactions, neutropenia, and pulmonary toxicity.

Sources: FDA press release. November 16, 2006.

New Engl J Med. 2005;353:1673–1684.

Long-Term Effects of Dexamethasone

Bacterial meningitis can lead to cognitive impairment, even after "good recovery." Dexamethasone, which has become a routine adjunctive treatment for the infection, has been associated with long-term adverse cognitive effects. Could it be compounding the problem? Researchers from the University of Amsterdam, Amsterdam, the Netherlands say the concern is unwarranted.

In a follow-up to the European Dexamethasone Study (a randomized, double-blind, placebo-controlled trial of adjunctive dexamethasone treatment in patients with suspected meningitis), they performed audiologic, neurologic, and neuropsychological testing on patients who had survived either pneumococcal or meningococcal meningitis a median of approximately eight years after discharge. Additionally, they recruited 50 healthy control subjects to undergo the same testing.

Of the 87 patients from the original study who were eligible, available, and willing to participate in the follow-up study, 46 had received dexamethasone and 41 had received placebo. Testing revealed that 17 patients (20%) had neurologic deficits and 11 (13%) had cognitive dysfunction (defined as three or more impaired test results on the neuropsychiatric examinations)—with no differences between the dexamethasone and placebo groups. Overall, patients who had survived bacterial meningitis were no more likely than control subjects to develop cognitive dysfunction. When comparing patients by causative organism, however, the researchers found that pneumococcal meningitis was associated with significantly more cognitive dysfunction and impairment of everyday functioning due to physical problems than meningococcal meningitis.

The researchers say their study comprises the largest long-term evaluation of patients with bacterial meningitis to date. They note that their findings suggest neuropsychological impairment improves in the first few years after bacterial meningitis and becomes relatively stable with time. ●

Source: *Ann Neurol.* 2006;60:456–468.