Drug Monitor

Anti-TNF Antibodies for RA: Effectiveness at a Cost?

Despite the "striking effectiveness" of tumor necrosis factor (TNF) inhibition as a therapy for rheumatoid arthritis (RA), a group of researchers from the Mayo Clinic College of Medicine, Rochester, MN and three centers in the United Kingdom (University of Leicester, Leicester; Institute of Public Health, Cambridge; and University of Manchester, Manchester) caution that this treatment may raise the risk of serious infections and malignancies. They conducted a meta-analysis of all randomized, placebo-controlled trials, published through December 2005, in which at least one of the two licensed anti-TNF antibodies (infliximab or adalimumab) was used for three months or longer in patients with RA.

Through an extensive literature search, the researchers identified nine trials that met the inclusion criteria, involving 5,005 patients. After reconciling any published adverse event data that conflicted with data reported to the FDA, they determined that 29 malignancies occurred in the 3,493 patients who received at least one dose of an anti-TNF antibody and three malignancies occurred in the 1,512 patients given placebo. In addition, 126 of the treated patients developed serious infections, compared with 26 of the placebo patients. Overall, patients treated with anti-TNF antibodies were more than three times as likely to develop malignancies and twice as likely to develop infections as placebo patients.

The review did not show an accumulation of malignancies with longer study duration. This could be explained, the authors suggest, by an acceleration of preexisting subclinical malignancies rather than induction, which should result in clusters of events with prolonged exposure to the study drug. Accordingly, they say, patients who are being considered for anti-TNF antibody treatment should be screened thoroughly for subclinical malignancies and monitored closely.

Using a low dose also might be a good idea, the authors add. They found that the increased risk of malignancies was dose dependent. Previous studies have shown that infliximab doses that exceed 3 mg/kg every eight weeks lead to a high risk of drug overexposure and excessive TNF binding. The differences in clinical efficacy between low dose and currently recommended higher doses were marginal and statistically insignificant. They also suggest further evaluation of the possibility of using anti-TNF antibodies as induction therapy only.

Source: *JAMA.* 2006;295:2275–2285.

Reducing Warfarin Interactions

It isn't uncommon for a patient who is prescribed warfarin to be taking other drugs—or for those drugs to have significant interaction potential, say researchers from Kaiser Permanente and Northwest Permanente, both in Portland, OR and Harvard Medical School and Harvard Pilgrim Health Care, both in Boston, MA. They point to a retrospective review that found 65% of patients taking warfarin received a concurrent prescription for at least one interacting drug that increased the risk of bleeding.

To evaluate the effectiveness of using electronic medical record (EMR) alerts to prevent such interactions in the outpatient setting, the researchers conducted an interrupted time series study involving 239 primary care providers at 15 clinics and 9,910 patients taking warfarin. The clinics received EMR alerts for the coprescription of warfarin and five interacting medications: acetaminophen, nonsteroidal anti-inflammatory drugs, fluconazole, metronidazole, and sulfamethoxazole. All of the alerts were clearly identified as safety alerts, included a short description of the clinical issue or risk, and recommended medication alternatives. Additionally, to determine if clinician education could improve the EMR alert effectiveness, seven of the clinics were chosen randomly to receive group academic detailing—one 40-minute session delivered to small groups that addressed barriers to the use of alerts.

At baseline, nearly one third of the patients had a prescription for one of the interacting study medications, the most common of which was acetaminophen. Coinciding with implementation of the alerts, the researchers found an immediate and continued decline in the prescribing of interacting medications, for a 15% relative reduction by month 12. Group academic detailing did not enhance alert effectiveness.

Coprescribing warfarin and interacting medications is not contraindicated in all situations, the researchers acknowledge. In fact, they say, acetaminophen alone or in combination with opioids often may be the best medication choice for pain in a patient taking warfarin. Similarly, the antibiotics targeted in the study might be the best or only choice in certain cases.

The researchers also note that their definition of coprescribing was conservative—that is, they counted a prescription overlap of even a single day. ●

Source: *Arch Intern Med.* 2006;166:1009–1015.