Drug Monitor

Protecting Patients with HCV from Lymphoma

Patients with hepatitis C virus (HCV) infection are reportedly at increased risk for malignant lymphoma. But does viral eradication with interferon therapy actually reduce this risk?

To find out, researchers from Toranomon Hospital in Tokyo, Japan performed a retrospective cohort study in which they analyzed data on 3,209 consecutive patients with chronic HCV from the hospital's hepatology database. Of these patients, 501 had never been treated with interferon and 2,708 had been treated with this drug.

The results suggested that interferon therapy does reduce the risk of malignant lymphoma—provided that it results in a sustained virologic response (SVR). None of the 1,048 patients who achieved an SVR with interferon therapy developed malignant lymphoma at five, 10, or 15 years after their first medical examination at the hospital. By contrast, the rates of lymphoma development among patients not treated with interferon were 0.6%, 2.3%, and 2.6% at five, 10, and 15 years, respectively. Similarly, patients whose HCV infection persisted (with or without interferon therapy) had lymphoma rates of 0.4%, 1.5%, and 2.6%, respectively. Overall, the hazard ratio for developing malignant lymphoma was 0.13 for SVR patients, compared with those who had persistent infection—a significant risk reduction ($P = .049$).

The researchers note that one patient in the SVR group eventually developed malignant lymphoma—approximately 20 years after the first examination and 466 days after completing interferon therapy. They are investigating whether this patient's cancer was de novo, caused by a genome mutation from HCV infection, or due to other factors.

Source: *Am J Med.* 2007;120(12):1034–1041. doi:10.1016/j.amjmed.2007.06.022.

Is Antithrombin III Helpful or Dangerous?

Antithrombin III, an anticoagulant with anti-inflammatory properties, is used widely in critically ill patients. But the medication's benefit to these patients is controversial, with four minor meta-analyses—only one of them a systematic review—failing to show that it improves mortality.

To help resolve this controversy, researchers from University of Copenhagen and Copenhagen University Hospital, both in Copenhagen, Denmark, performed a more ambitious meta-analysis and systematic review. They gathered every full-paper, randomized trial they could find that compared the mortality of critically ill patients who took the medication to that of critically ill patients who took placebo or had no intervention. And they used these trials—first by pooling all of their populations and then by breaking these populations into several subgroups—to investigate antithrombin III's impact on mortality and several secondary outcomes.

The researchers found 20 trials, involving a combined total of 3,458 patients, that met their inclusion criteria. These trials used sample sizes ranging from 25 to 2,314 patients, antithrombin III regimens ranging from a single bolus to 14 days of administration, and follow-up periods ranging from seven to 90 days. Thirteen of the trials studied patients with sepsis, three studied pediatric patients, two studied obstetric patients, and two studied trauma patients. Eight of the trials were found to have a low risk of bias, as defined by adequate randomization procedures, blinding, and intention-to-treat analysis. And one of these low-bias trials dominated the meta-analysis—it contributed 80% of the researchers' information.

The trials' pooled results showed that antithrombin III had no significant effect on mortality rate, which was 39% in patients who took the medication and 40% in those who did not. It also had no significant effect on the incidence of respiratory failure, duration of mechanical ventilation, need for surgical intervention, or length of stay in a hospital or intensive care unit. Moreover, the results showed that antithrombin III increased patients' risk of bleeding events.

All of these findings persisted when the trials' pooled population was broken into subgroups according to type of patient, length of trial, length of follow-up period, and inclusion in a trial with or without a low risk of bias. The only subgroup that appeared to benefit from antithrombin III consisted of patients who did not receive adjuvant heparin—a standard treatment for disseminated intravascular coagulation. But while a fixed effects model indicated that this subgroup's mortality rate decreased significantly in response to antithrombin III, a random effects model indicated no such decrease.

Overall, the researchers conclude, antithrombin III cannot be recommended for critically ill patients. They say that while this judgment extends to patients who are not taking heparin, future trials may want to explore the interactions between antithrombin III and heparin. ●

Source: *BMJ.* 2007;335(7632):1248–1251. doi:10.1136/bmj.39398.682500.25.