Trial watch

CHEMOPREVENTION WITH COX2 INHIBITORS?

Colorectal cancer often develops from adenomatous polyps (adenomas), so finding agents that can prevent or regress colorectal adenomas has been a goal of researchers. Cyclooxygenase 2 (COX2) is overexpressed in human colorectal adenomas and tumours, but not in normal colorectal tissue, indicating that COX2 inhibitors might prevent colorectal cancer.

The primary results of two large trials that investigated the use of the COX2 inhibitor celecoxib for the prevention of colorectal adenomas were reported recently. These trials were both stopped in late 2004 following reports that celecoxib and other COX2 inhibitors could increase the risk of cardiovascular events. Although the safety data from these trials were published rapidly, it was not possible to assess the risk–benefit ratio of celecoxib for chemoprevention until now.

The placebo-controlled Adenoma Prevention with Celecoxib (APC) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials were similarly designed, and randomized 2,035 and 1,561 patients, respectively. Only patients who had had an adenoma removed during a previous colonoscopy were enrolled, and both trials were planned to have 3 years of active treatment with colonoscopies after 1 and 3 years. Different dosing regimens were used; patients in the APC trial received 200 mg or 400 mg of celecoxib twice a day or placebo, and patients in the PreSAP trial received 400 mg of celecoxib once a day or placebo.

Both trials found that celecoxib was significantly more effective than placebo for preventing adenomas over 3 years of treatment. In the APC trial, the cumulative incidence of adenomas was 60.7% for patients who received placebo, and 43.2% and 37.5% for patients who received 200 mg or 400 mg of celecoxib twice a day, respectively. In the PreSAP trial, the cumulative incidence of adenomas was 49.3% in the placebo group and 33.6% in the celecoxib group. Both trials were too small to assess whether celecoxib decreased colorectal cancer rates, but reduction in adenoma is considered an excellent surrogate endpoint for colorectal cancer.

However, both trials also found that celecoxib was associated with an increased risk of cardiovascular events compared with placebo. A hypothetical risk–benefit analysis in an accompanying editorial suggested that celecoxib could have an advantage over no treatment for preventing colorectal cancer. However, because cardiovascular events are much more common than colorectal cancer, the increase in cardiovascular events with celecoxib clearly outweighed any possible decrease in colorectal cancer.

So, although celecoxib can prevent colorectal adenomas, it cannot be recommended for this indication owing to an increased risk of cardiovascular events.

ORIGINAL RESEARCH PAPERS Arber, N. *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N. Engl. J. Med.* **355**, 885-895 (2006) | Bertagnolli, M. M. *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N. Engl. J. Med.* **355**, 873–884 (2006)
FURTHER READING Psaty, B. M. & Potter, J. D. Risks and benefits of celecoxib to prevent recurrent adenomas. *N. Engl. J. Med.* **355**, 950–952 (2006)