Research Update • Le point sur la recherche

Controversial study of thalassemia drug ends early

A new drug developed to treat the iron overload resulting from thalassemia major fails to do so adequately and may even worsen hepatic fibrosis caused by iron, a study has concluded (*N Engl J Med* 1998;339:417-23).

Thalassemia major (Cooley's anemia) is a serious homozygous inherited disorder of globin chain synthesis that causes ineffective red-blood-cell formation, severe anemia, splenomegaly and enlargement of the cranial and facial bones. An estimated 180 million people around the world are heterozygous for the gene. They are usually asymptomatic or have a mild anemia. Most patients are of Mediterranean, Asian or African descent.

Although patients with thalassemia can avoid most of the disease's effects by undergoing blood transfusions from a young age, the frequent transfusions can eventually cause iron loading, which can lead to death, usually from heart disease. Iron overload may also lead to the development of cirrhosis, diabetes mellitus or adrenal insufficiency, and result in failure to mature sexually. Patients are treated with agents to remove the excess iron and prevent these complications. For the past 25 years, the gold standard in treatment has been subcutaneous deferoxamine therapy. Recent studies indicate that more than 90% of patients who take the drug as prescribed survive without heart disease and with minimal toxic effects. However, the drug regimen is expensive and onerous. To receive the drug, patients must be hooked up to infusion pumps 12 hours day, 4 to 6 days per week, and this results in noncompliance.

Researchers therefore began looking for an equally efficacious drug that is easier to use. Deferiprone, an oral medication, was considered a candidate. In a study carried out at the Hospital for Sick Children in Toronto, patients were given either the new drug or deferoxamine to treat iron overload. Hepatic iron stores were determined annually by chemical analysis of liver-biopsy specimens, magnetic susceptometry, or both. The hepatopathologists were blinded to the patient's clinical status.

Publication of the paper has proved controversial because the lead author, Dr. Nancy Olivieri, had signed a contract with a company that allowed it to veto publication of results. The political and ethical issues lying behind the research are complicated, and these issues will be explored in a future issue of *CMAJ*. However, Olivieri says the scientific facts are straightforward. "It was not effective in most patients and it now appears to be toxic in another group," she says. In 18 patients treated with deferiprone for an average of 4.5 years, 7 (39%) had iron concentrations above the threshold for risk of cardiac disease and early death.

Hepatic fibrosis could be evaluated by liver biopsy in 14 of the patients receiving deferiprone and in 12 of those taking deferoxamine. These evaluations indicated that fibrosis had progressed in 5 of the patients receiving deferiprone but none of those receiving deferoxamine — a statistically significant difference. Analysis showed that the odds of fibrosis progression increased by a factor of 5.8 with each additional year of deferiprone treatment. The researchers estimated that the median time to progression of fibrosis in the deferiprone-treated patients was 3.2 years. The researchers concluded that deferiprone does not control the body iron burden adequately in patients with thalassemia and may worsen hepatic fibrosis.

However, an editorial in the same issue of the *New England Journal of Medicine* urged caution in reaching conclusions based on this study. "There were important differences between the deferiprone-treated patients in whom fibrosis worsened and those in whom it did not, and these differences could influence the progression of fibrosis." — *C.J. Brown, Barbara Sibbald*

In the news . . .

Genetic ovarian cancer and the pill

Oral contraceptives provide some protection against ovarian cancer, with a new study indicating that the pill is particularly useful for cutting the risk for women with mutations in the *BRCA1* and *BRCA2* genes (*N Engl J Med* 1998;339:424-8). The case–control study showed that any previous use of oral contraceptives cut the risk of ovarian cancer by half for women at high risk and that long-term use — more than 6 years — lowered the risk by 60%.

How the thermometer resets the clock

The circadian "clock" within all organisms controls many physiologic responses. It was thought that light and darkness triggered the clock as day turned to night and back to day. However, experiments in fungi show that even moderate temperature shifts activate clock proteins (*Science* 1998;281:825-9). In fact, raising or lowering the temperature can reset the circadian clock almost immediately, regardless of light conditions or even in opposition to them.