Drug Monitor

Hydroxyurea vs. Anagrelide in Essential Thrombocythemia

The clonal hematologic stem cell disorder essential thrombocythemia predisposes patients to thrombosis (particularly arterial); can sometimes cause hemorrhage; and may progress to myelofibrosis, myelodysplasia, or acute myeloid leukemia. While both hydroxyurea and anagrelide have been used widely as first-line therapies—often with low dose aspirin—in these patients, anagrelide is more expensive and previous studies have raised concerns about efficacy.

To find out how the drugs performed head-to-head, researchers from the United Kingdom Medical Research Council Primary Thrombocythemia 1 study compared hydroxyurea plus aspirin with anagrelide plus aspirin in 809 patients with essential thrombocythemia who were at high risk for thrombosis. The open-label, randomized trial extended over a 12- to 72-month period. The patients, enrolled from 138 centers in the United Kingdom, Ireland, and Australia, all had one or more of the following risk factors for thrombosis: age 60 years or older; current or previous platelet count of 1,000,000 cells/mm^3 or more; history of ischemia, thrombosis, or embolism; previous hemorrhage due to their thrombocythemia; or treatment for hypertension or diabetes.

While both treatments resulted in equivalent long-term control of platelet counts, hydroxyurea plus aspirin was associated with significantly lower rates of arterial thrombosis, serious hemorrhage, transformation to myelofibrosis, and treatment withdrawal. On the other hand, the rate of venous thromboembolism was significantly lower in the anagrelide plus aspirin group.

The researchers advise that optimal treatment of patients with prior venous thrombosis will depend on individual circumstances, but they also note that arterial thrombosis is more than three times more common than venous thrombosis in essential thrombocythemia. The fact that both treatments achieved similar platelet control while resulting in different outcomes, they say, implies that either hydroxyurea or anagrelide may modulate thrombosis by additional mechanisms besides lowering the platelet count. They suggest that the lower white cell count seen in patients receiving hydroxyurea may be relevant, since white cells contribute to the procoagulant response.

They also point out that the higher incidence of serious hemorrhage with anagrelide may reflect a synergistic effect of the drug and aspirin on platelet function. If anagrelide is used, they say, concurrent aspirin therapy should depend on the patient's relative risk of arterial thrombosis and hemorrhage.

Source: *N Engl J Med.* 2005;353:33–45.

Treating Hospital-Acquired Malnutrition

How helpful is megestrol acetate for elderly patients with hospital-acquired malnutrition? Given the inconclusive results of the few previous studies that have been conducted, researchers from the University of California, Los Angeles decided to perform a randomized, nine-week, phase II clinical trial comparing three doses of megestrol acetate with placebo in 47 patients aged 60 and older who had been discharged recently from an acute care hospital with a fair or poor appetite.

The hope was to find a dosage that would have the best effect on nutrition with the least toxicity. The only published clinical trial data involving older people had showed modest benefits at 800 mg/day, a dose considered optimal for patients with AIDS. Because elders have a higher percentage of body fat than younger people, and since megestrol is stored in fat, the researchers chose two lower doses as well: 400 mg/day and 200 mg/day.

A total of 45 patients completed the trial. While there were no significant differences between the groups on any of the appetite measures, the 800-mg group described their appetite as having improved over baseline at 20 days, and the 400-mg group reported similar improvement at 42 days.

At 20 days, prealbumin levels increased in a dose-response manner across all four groups, with the increases in the 400- and 800-mg groups (34% and 48%, respectively) being significantly higher than that in the placebo group. By day 63, however, only increases in the 400-mg group maintained statistical significance.

At 20 days, patients in the 400- and 800-mg groups had significantly lower cortisol levels than those assigned to placebo. The clinical significance of low cortisol levels associated with megestrol is unknown, the researchers say. No patient developed adrenal insufficiency. Three patients (from the 400- and 800-mg groups) had diarrhea, and two (one each from the 200- and 400-mg groups) developed thromboembolism.

The researchers concluded that, other than the rise in prealbumin levels, megestrol acetate didn't confer a nutritional or clinical benefit over placebo. If the drug is used, they say, the 400- and 800-mg dosages are most likely to be helpful, but they advise larger phase III trials before recommending the drug to this population.

Source: *J Am Geriatr Soc.* 2005;53:970–975.

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How Valuable Are Short-Acting Insulin Analogs?

Compared to regular insulin, short-acting insulin analogs have only a small, statistically significant, beneficial effect on glycosylated hemoglobin (HbA_{1C}) values in adults with type 1 diabetes—and no benefit at all in patients with type 2 or gestational diabetes, say researchers from Medical University and the Institute of Medical Technologies and Health Management, Graz, Austria and Landeskrankenhaus, Hörgas, Austria. They evaluated data from 42 randomized, controlled trials comparing these analogs with regular insulin in 7,933 patients with type 1, type 2, or gestational diabetes.

They found no trials that compared long-acting insulin analogs, insulin glargine, or insulin detemir to regular insulin. Thus, they say, it remains an open question whether the concurrent use of short- and long-acting insulin analogs will attain results comparable to continuous subcutaneous insulin infusion.

The researchers also found no study designed to investigate long-term effects. They say it seems unlikely that the magnitude of improved glycemic control observed in analog treatment compared with regular insulin treatment (overall, a 0.12% reduction in HbA_{1C} among adults with type 1 diabetes) will prevent the development and progression of microvascular complications. Also, despite potentially adverse properties of insulin analogs, such as possible mitogenic effects, they found no data concerning long-term safety. Furthermore, they caution that patients with clinically advanced microvascular complications have been excluded from most clinical studies.

Short-acting insulin analogs have been touted for improving patients' quality of life (QOL). In the meta-analysis, QOL advantages for these analogs mainly concerned flexibility, convenience, and continuity of treatment administration—and largely depended on comparison to a fixed interval of 30 minutes for premeal injection of regular insulin. The researchers note, however, that in actual situations, most patients taking regular insulin don't follow a 30-minute rule, and the only double-blinded study found no improvements in QOL, metabolic control, or overall hypoglycemia.

In order to assure the safety of short-acting insulin analogs, the researchers conclude, long-term follow-up of large numbers of patients are needed, along with well designed studies in pregnant women.

Source: *Arch Intern Med.* 2005;165:1337–1344.

Hypersensitivity to Once Daily Abacavir

Anything that can help reduce the "pill mountain" that patients with HIV face is welcome, so it's good news that abacavir can be taken once a day, rather than twice. The bad news, however, is that researchers from Iowa Drug Information Network and the University of Iowa, both in Iowa City say there might be a greater chance of severe hypersensitivity reactions with the once daily regimen.

Abacavir has been known to cause life threatening hypersensitivity reactions rarely (in about 8% of patients in clinical trials). Among the studies the researchers reviewed, only one double-blind, randomized, controlled trial compared the two abacavir regimens. This study (known as CNA30021) showed a significantly higher risk of severe hypersensitivity reactions with the once daily regimen; open-label comparisons found no significant differences. Given this discrepancy, the researchers say, more evidence is needed to determine the level of risk.

In the meantime, the researchers conclude that the convenience of once daily abacavir is an advantage that must be weighed carefully against the potential risks. They advise that all patients taking abacavir be made aware of the possibility of severe hypersensitivity reactions. If such a reaction occurs, abacavir should be stopped and not reintroduced, since the symptoms will recur and rapidly become life threatening.

Source: *Ann Pharmacother.* 2005;39:1302–1308.

rt-PA for Stroke: Why the Reluctance?

Despite favorable results from the National Institute of Neurological Disorders and Stroke (NINDS) trial and FDA approval, the use of recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke has remained controversial among physicians in the emergency department, and only 1% to 2% of patients who have a stroke are treated with the drug. Given that stroke remains the number one cause of adult disability in the United States, researchers from the University of Michigan Health System, Ann Arbor and the American College of Emergency Physicians, Dallas, TX surveyed 2,600 randomly selected members of the American College of Emergency Physicians to find out how many were resistant to the idea of using rt-PA and why.

Of the 1,105 respondents, 40% said they were unlikely to use rt-PA for stroke: 65% because of concerns about the risk of symptomatic intracerebral hemorrhage, 23% because of concerns about efficacy, and 12% for both reasons. Female respondents were more likely to be willing to use rt-PA, as were respondents who had previously used the drug for stroke.

When asked what they considered the highest risk of symptomatic intracerebral hemorrhage acceptable for treatment, the mean response was 3.4%—compared with the actual 6.4% risk found in the NINDS stroke trial. When only those respondents resistant

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to using the drug were considered, this threshold dropped to 2.1%. The mean lowest acceptable relative improvement with treatment was 40% among all respondents and 45% among resistant respondents. In the NINDS trial, the relative benefit seen with rt-PA was 30% to 50%, depending on the functional outcome measured.

In light of these findings, the researchers suggest that future treatment trials aim to reduce the risk of symptomatic intracerebral hemorrhage to between 2% and 3%, while maintaining the expected benefit seen with the current rt-PA protocol. Whether this can be achieved through modifying rt-PA regimens or through the use of other thrombolytic agents remains to be seen. ●

Source: *Ann Emerg Med.* 2005;46:56–60.