

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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EXPERIMENTAL MEDICINE

Effects of Recombinant Apolipoprotein A-1 on Coronary Atherosclerosis

Plasma levels of HDL-cholesterol and its major protein (apoA-1) are inversely associated with coronary heart disease risk in observational studies. Studies in laboratory animals have established that genetic overexpression of apoA-1 can substantially reduce the progression or even induce regression of preexisting atherosclerosis. Intravenous infusions of HDL or apoA-1 also appear to be protective in animals. Based on these data, HDL and apoA-1 have become an important target for development of new therapies for atherosclerosis [*JAMA* 290:2322-24].

Finding small molecules that upregulate the gene expression of apoA-1 has been an elusive goal of pharmaceutical research. The idea of giving HDL itself has been in the public domain for many years and, thus far, pharmaceutical companies have evinced no interest. Some researchers, however, have persevered and a recent report in *JAMA* [2003;290:2292-300] provides a stunning demonstration of the potential of this strategy. The current story starts more than 20 years ago.

In 1980, investigators reported on a family from a small village in northern Italy in which three members had very low HDL-C levels (< 15 mg/dl) but had no clinical signs of premature atherosclerotic disease. These people carried a naturally occurring variant of apolipoprotein A-1 called ApoA-1 Milano, which differs from the native protein, in that cysteine is substituted at position 173 for arginine. Further investigation identified 34 other people in the village who carried mutant apoA-1. The researchers determined that these people were not at the increased risk of premature CHD that might be predicted on the basis of their very low HDL levels.

Recombinant ApoA-1 Milano has been formulated in a complex with naturally occurring phospholipids. The resulting product is designated ETC-216. Animal studies showed that the complex rapidly mobilized cholesterol and reduced atherosclerotic plaque. These data led to the development of recombinant ApoA-1 Milano as a potential therapeutic approach for atherosclerosis in humans.

Investigators hypothesized that short-term weekly infusions of ETC-216 might regress coronary atherosclerosis in patients following an acute coronary syndrome. To test this hypothesis, they conducted a blinded, controlled trial of ETC-216 using ultrasound to measure atheroma burden in coronary vessels.

Patients who received five weekly infusions of ETC-216 demonstrated significant regression in coronary atheroma volume in the target segment com-

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EXPERIMENTAL MEDICINE (continued)

Recombinant Apolipoprotein A-1 and Coronary Atherosclerosis (continued)

pared with baseline measurements. A placebo group that received only saline infusions had no significant change in atheroma volume. The absolute change in atheroma volume in the treatment group was a 4.2% decrease from baseline. Although the findings are promising, the researchers caution that their results require confirmation in large clinical trials with morbidity and mortality endpoints.

An accompanying editorial points out several important limitations to the interpretation of the study. The study was not designed or powered to compare the treatment group with the control group, only with baseline values. Consequently, there was no statistically significant difference between them. Furthermore, the administration of a saline placebo rather than phospholipids alone, leaves open the possibility that the regression seen in the active treatment group

was due to the phospholipid rather than the ApoA-1 Milano component. In addition, two different doses of ETC-216 were used but no evidence of a dose-response was seen. Finally, the study was small (45 patients receiving ETC-216 and 12 receiving placebo).

Nevertheless, the author of an accompanying editorial concludes that the results suggest that the regression in the treatment group was likely to be a direct result of the ETC-216 infusions. He adds, "This study provides the best example to date that directly targeting HDL can have an impact on atherosclerosis in humans" [JAMA 2003;290:2322-24]. An intriguing question, as yet unanswered, is whether ApoA-1 Milano has biological properties that make it more effective than normal wild-type apoA-1 in preventing or regressing atherosclerosis.

CLINICAL PRACTICE

Strict Diet versus Statin on Serum Lipids and C-Reactive Protein

A diet rich in fiber and soy protein lowered total and LDL cholesterol about as much as did lovastatin in a recently reported study [JAMA 2003;290:502-10]. Most dietary manipulations result in modest cholesterol reduction of 4% to 13%, and diet has been considered by some as a relatively ineffective therapy. This is the first demonstration that a very strict diet might provide benefits similar to those observed with cholesterol-lowering drugs.

The study enrolled 46 healthy, hyperlipidemic adults with a body mass index of 27.6. The participants had total cholesterol levels of 250-260 mg/dl and LDL cholesterol levels greater than 160 mg/dl. Patients were randomly assigned to undergo one of three interventions on an outpatient basis for one month: a diet low in saturated fats (control); the same diet plus lovastatin 200 mg daily; or a very strict diet high in plant sterols, soy proteins, fiber (oats and barley), and almonds.

The control group, statin group, and very strict diet group had mean decreases in LDL cholesterol of 8%, 30.9%, and 28.6%. Respective reductions in C-reactive

protein were 10%, 33.3%, and 28.2%. The author of an editorial accompanying the report says that, if confirmed in other investigations, these findings have far-reaching implications for a large number of patients with dyslipidemia. While recognizing that adherence to strict and intensive dietary management requires motivation by patients, encouragement, and counseling, he maintains: "For most patients, dietary intervention should be the first line of therapy (perhaps for 6 to 12 weeks) before introducing pharmacotherapy for hyperlipidemia [Ibid, 531-33]."

The principal investigator told *The Wall Street Journal Online* [23 July 2003] that the study "shows there are ways now of lowering cholesterol using a combination of foods that are as effective as the first generation of statins." However, there are important limitations of the research. The diet used in the study is an extreme and Spartan one—strictly vegetarian with an abundance of soy and fiber—that many people may not be able to follow over the long term. The results of a six-month study of the intervention

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Diet vs. Statin on Serum Lipids and C-Reactive Protein (continued)

might be dramatically different than the results from this one-month study. The lead investigator acknowledged that it was a “fair comment” that much of the diet would be too extreme for many people. But he

also noted that some of the diet, such as almonds, was quite palatable. The study was funded in part by the Canadian government and the Almond Board of California.

Does Lowering Plasma Homocysteine Decrease Risk?

A recent issue of *The Medical Letter* [2003;45:85-86] tackled this timely question. High homocysteine concentrations have been associated with an increased risk of cardiovascular disease and death. Whether high levels of homocysteine are a cause, a marker, or a consequence of atherosclerosis is unknown. Some studies have suggested that homocysteine could damage vascular endothelium.

Although a threshold level for normal plasma homocysteine has not yet been established, the nutrition committee of the American Heart Association considers it desirable to have a fasting concentration of less than 10 $\mu\text{mol/l}$. Serum concentrations of folate, vitamin B₆, and vitamin B₁₂ are inversely related to plasma homocysteine concentrations. Randomized trials suggest that administration of folate lowers homocysteine levels by about 25%; adding B₁₂ lowers levels somewhat more. Folate is found in a wide range of foods, but daily intake by the average American may not be sufficient to adequately lower high homocysteine concentrations.

Studies of the effects of administering folate and the other vitamins as supplements to patients with coro-

nary artery disease have led to mixed results. Angioplasty patients, about half of whom received stents, who took a daily combination of folate (1 mg), along with vitamin B₆, and vitamin B₁₂ for six months, had a 20% rate of restenosis compared with 38% of those who received placebo, and a lower rate of revascularization (11% vs. 22%) [*N Engl J Med* 2001;345:1593-600]. However, a similar study, described at the American College of Cardiology Annual Meeting 2003, found higher rates of restenosis associated with folate supplementation. In another recent study, in patients with stable coronary artery disease, folate 5 mg/day reduced homocysteine levels but had no effect on the incidence of cardiovascular events and death [*J Am Coll Cardiol* 2003;41:2105-13]. Other studies are ongoing.

The Medical Letter associates concluded, “Trying to lower plasma homocysteine concentrations to prevent coronary disease seems premature. There is no convincing evidence to date that such a practice is beneficial, and it may not necessarily be harmless.”

Massachusetts to Establish Quantity Limit for Short-Acting Beta-Agonists

Massachusetts Medicaid will establish a quantity limit for short-acting beta-agonists to encourage physicians to provide adequate anti-inflammatory therapy with inhaled corticosteroids. Under the program’s Asthma Provision, the state advises that the use of more than one canister per month of a short-acting beta-agonist may indicate inadequate control and the need for initiating or intensifying anti-inflammatory therapy.

A one-canister-per-month benchmark is consistent with guidance provided by the National Asthma Education & Prevention Program Expert Panel. The asthma initiative also includes changes to the program’s prior authorization requirements. Based on physician feedback, the state said it will no longer

require prior authorization for patients requiring treatment with both a beta-agonist and a corticosteroid, a foolish hurdle in the first place.

However, the program now mandates prior authorization for use of several oral asthma therapies including zafirlukast (*Accolate*), montelukast (*Singulair*), and zileuton (*Zyflo*) for patients older than 16 if, over the last six months, the patient has not filled a prescription for an inhaled short- or long-acting beta-agonist or corticosteroid. Massachusetts hopes the requirements will control both on- and off-label use of the leukotriene blockers for allergies; only *Singular* carries an indication for allergic rhinitis.

DRUG EVALUATION

Treatment Interruption May Worsen Course of Drug-Resistant HIV Infection

The best therapeutic approach to patients infected with multidrug-resistant HIV that does not respond to treatment is uncertain. Investigators and clinicians have increasingly flirted with interruptions of antiretroviral therapy to overcome treatment failure and to help manage the toxic effects of therapy. Although treatment interruption may lead to a decline in the CD4 cell count and an increase in viral load, it has also been associated with the reemergence and predominance of a more sensitive (wild-type) viral population in patients with multidrug-resistant HIV. Some studies have suggested that this strategy may result in a better virologic response when treatment is reinitiated. However, more recent and better-controlled studies have reported conflicting results. A rather definitive evaluation of the benefits and risks of treatment interruption is now available [*N Engl J Med* 2003;349:937-46].

In the study, patients with multidrug-resistant HIV and HIV RNA levels of more than 5000 copies/ml were randomly assigned to a four-month interruption of treatment followed by a change to an optimized antiretroviral regimen or to an immediate change in regimen (control group). After a median of 11.6 months, disease progression or death occurred in 22 of the 138 patients in the treatment-interruption group and in 12 of 132 patients in the control group, with a hazard ratio of

2.57 for the treatment-interruption group. There were eight deaths in each group.

In the treatment-interruption group, the mutant HIV population completely or partially reverted to wild-type by four months in about two-thirds of patients. Mean HIV RNA levels, as expected, climbed during treatment interruption, but subsequently fell below baseline and were similar to mean levels in the control group. CD4 cell counts, on the other hand, fell during treatment interruption and continued to lag behind counts in the control group through eight months. The overall quality of life was similar in the two groups. Thus, interruption of treatment with antiretroviral drugs leads to greater disease progression without conferring any benefits. Continuing therapy guided by HIV resistance testing appears to be a better approach.

In an NIH press release, Dr. Anthony Fauci advises against dropping the concept of treatment interruption entirely. He notes that it is important to remember that the failure of treatment interruption seen in this study applies only to individuals who had drug-resistant HIV and high levels of virus in their blood when they enrolled in the study. Dr. Fauci added, "For individuals who are being successfully treated with anti-HIV medications, other studies have shown cycles of treatment interruptions for shorter periods may be of potential benefit to conserve medications and reduce drug-related toxicities" [*Reuter's Health*, 28 August 2003].

Carvedilol Versus Metoprolol Revisited

In a study called COMET [*Lancet* 2003;362:7-13], a randomized trial of 3029 patients with chronic heart failure, carvedilol reduced mortality by 17% relative to metoprolol. The estimated increase in life expectancy achieved with carvedilol was 1.4 years on average. The findings were presented as a pharmacological triumph for carvedilol over metoprolol [*Ibid*, 2-3].

Before this conclusion is endorsed, however, the question of dose has to be considered. Doses in COMET aimed for comparable reductions in resting heart rate between the two groups. The heart reduction in the patients receiving carvedilol at a

target dose of 25 mg twice daily was 13 beats per minute. However, the heart rate reduction with the target dose of 50 mg twice daily of metoprolol (actual mean dose of 85 mg/day) was only 11.7 beats per minute, compared with 15 beats per minute seen in an earlier study with metoprolol at a dose of 150 mg/day (actual mean dose of 108 mg/day). In yet another study, using an extended-release formulation of metoprolol, a target dose of 200 mg/day (actual mean dose of 106 mg/day) resulted in a heart rate reduction of 14 beats per minute. The mortality reduction in these earlier trials was about the same as

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DRUG EVALUATION (continued)

Carvedilol Versus Metoprolol Revisited (continued)

the mortality reduction in COMET patients who received carvedilol.

Thus, the results of COMET are not the final word as to which β -blocker is best in the chronic treatment of heart failure. One is not assured that in

COMET, metoprolol, at the doses employed, exerted a similar degree of β -blockade to carvedilol. Furthermore, in future trials, the widely prescribed extended-release form of metoprolol should be the comparator (*Thanks to Dr. Andrew Coveler for bringing this to our attention*).

DRUG SAFETY

Venous Thrombosis Risk Lower with Transdermal Rather than Oral Estrogen

A recently reported study highlights the importance of route of administration in assessing the safety of menopausal hormone therapy. Oral hormone therapy induces activated protein C (APC) resistance, a risk factor for venous thromboembolism, and activates blood coagulation. Whether transdermal hormone therapy poses a similar risk is not known. Accordingly, investigators conducted a randomized, placebo-controlled trial that assessed the effect of both oral and transdermal estrogen/progestin regimens on the anticoagulant response and on coagulation activation [*Arterioscler Thromb Vasc Biol* 2003;23:1671-76].

They randomly assigned 196 postmenopausal women to placebo or to oral estradiol or transdermal estradiol, both combined with oral micronized progest-

erone for six months. Oral but not transdermal estrogen significantly altered the effect of APC on thrombin generation, leading to an acquired APC resistance. After six months, plasma markers of coagulation activity were significantly higher in the oral estrogen arm than in the transdermal or placebo arms. These data provide a plausible biologic mechanism for the demonstrated association between oral estrogen and venous thrombosis. The study also provides biologic evidence that suggests a lower risk for venous thrombosis, if any, among users of the estrogen skin patch. Indeed, a case-control study published in the *Lancet* in August determined that current users of oral estrogen were four times more likely to develop venous thromboembolism than current users of transdermal estrogen [*Lancet* 2003;362:428-32].

NSAIDs and Miscarriage

While NSAIDs are relatively safe, their use during pregnancy could pose problems for the mother and fetus. An observational study suggested a possible link between NSAID use and miscarriage. To further explore this proposed link, researchers performed a prospective cohort study to assess risk factors for miscarriage [*BMJ* 2003;327:368]. Data were collected on the use of NSAIDs, aspirin, and acetaminophen.

Overall, among 1055 women included in the final analysis, 75 were identified as users of NSAIDs or aspirin. These women, as a group, were more likely to have consumed coffee and alcohol, smoked, used a hot tub, and taken multivitamins since their last menstrual period. After adjustment for these confounders, the investigators found that the use of NSAIDs during preg-

nancy increased the risk of miscarriage by 80%. A higher risk was found when the NSAID was taken around conception (adjusted hazard ratio, 5.6) or was used for longer than one week (adjusted hazard ratio, 8.1). The risk of miscarriage associated with aspirin use during pregnancy followed a similar pattern, but the association was weaker. The use of acetaminophen was not associated with risk of miscarriage.

Commentary in the *Prescriber's Letter* [2003; 19:191012] observes that results of both studies are consistent with findings from animal studies, which indicate that NSAIDs might block implantation of the embryo into the uterine wall because prostaglandins are needed for this process. Since NSAIDs and aspirin are prostag-

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DRUG SAFETY (continued)

NSAIDs and Miscarriage (continued)

landin inhibitors, they could, in theory, prevent successful embryo implantation, resulting in miscarriage. Despite these concerns, some women benefit from low-dose aspirin during pregnancy, including those with antiphospholipid antibodies and those at high risk for preeclampsia. There is no reliable information concerning the use of low-dose aspirin and the risk of miscarriage. In some pregnant women, benefit may outweigh harm.

In addition to the possible link to miscarriage, the use of NSAIDs and full-dose aspirin has been associated with prolonged gestation and labor, increased anemia, and increased peripartum blood loss and risk of hemorrhage in the mother, as well as premature closure of the ductus arteriosus, persistent pulmonary hypertension, impaired renal function, and an increased risk of intracranial hemorrhage in the fetus.

FDA Advisory on Antidepressants in Young Users

The FDA, concerned about reports of suicidal ideation and suicide attempts among adolescents and children who have taken antidepressants during drug trials, has asked physicians to be alert to such incidences. However, even as it sent out the advisory, the agency stressed that it was doing so out of caution—not because a link has been established between the use of antidepressants and suicide attempts [*The Wall Street Journal Online*, 28 October 2003].

Commenting on the clinical trials that have raised concerns, the agency noted that only a minority of 20

studies has shown a small increase in suicide ideation and attempts in adolescents on the drugs, compared with young people on placebo. There were no successful suicides in any of the trials. Indeed, the absolute suicide rate in the broader population has been falling in recent years while use of antidepressants has increased. A paper published in the October issue of *General Psychiatry* reported that, when antidepressant use rose in different regions of the country, the suicide rate among youths aged 10 to 19 dropped. Most experts think that the FDA's caution is appropriate but do not believe that the scattered reports pose a problem.

CONTROVERSIES AND DILEMMAS

Widening Use of Opioids for Chronic Nonmalignant Pain

Through marketing efforts of drug manufacturers, many clinicians are getting the message that opioid drugs are an effective therapy for chronic, noncancer pain. Proponents say that the use of opioids for nonmalignant pain is appropriate and long overdue, but critics caution that little is known of adverse effects of long-term use.

Presenting his views at the annual scientific meeting of the American Pain Society in March, an advocate of broader use stated that multiple survey studies show long-term benefit without significant risks such as tolerance, addiction, persistent adverse effects, and impairment in physical and psychosocial functioning, but he conceded the limitations of nonrandomized survey data.

Opioids are a booming business for the pharmaceutical industry with a reported \$3 billion in annual sales. Sales exploded in the 1990s when research suggested addiction and tolerance fears were overstated. Even though the use of opioids in noncancer patients has

become more accepted, such fears continue to linger and are at least partially responsible for underuse of opioids for patients with pain. This is unfortunate. A recent study analyzing data on medical opioid use found that abuse levels remained low despite increases in use between 1990 and 1996. This, however, has not quieted the critics.

Research on the long-term effects of opioid treatment has been hobbled by lack of interest among epidemiologists and academicians, due at least in part to poor funding from pharmaceutical companies and the federal government. A more important impediment to appropriate use of opioids in managing chronic pain is the reluctance of physicians and patients to choose rehabilitation because it is time consuming and slow to provide benefit. Indeed, opioids do not relieve pain in up to 40% of patients and rehabilitation offers the possibility of eliminating the source of pain and not just masking it [*JAMA* 2003;289:2347-49].