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Efficacy of Vytorin and Zocor: The ENHANCE Trial by Sarah Judd

Data regarding the ENHANCE trial have recently had health care professionals and patients asking themselves if ezetimibe (Zetia), an agent that fights cholesterol by inhibiting its absorption in the gut, is a worthwhile agent to help reduce risk of plaque buildup in the vascular system.

The ENHANCE study, sponsored by Merck-Schering-Plough, studied 720 patients with Heterozygous Familial Hypercholesterolemia (HeFH).¹ Roughly 1 in 500 people have this genetic disorder that is caused by mutations in the LDL receptor, ultimately causing LDL levels > 250mg/dL, on average.² Patients were given 80mg of simvastatin (Zocor) or the combination treatment of ezetimibe/simvastatin (Vytorin) 10/80mg daily for two years. The purpose of the study was to evaluate plaque buildup in three distinct sites of the carotid arteries, which was assessed by an ultrasound at 6, 12, 18, and 24 months.¹ No significant differences in *baseline* LDL cholesterol levels (319 vs. 318 mg/dL) or carotid intima-media thickness (IMT) existed between the two treatment arms.

After two years, no significant difference in IMT was shown in the ezetimibe/simvastatin group (0.0111 mm) compared to the simvastatin group (0.0058 mm), $P=0.29$. Despite this nonsignificant difference in plaque buildup, there was still a significant reduction in LDL with the combination treatment group (58%) compared with the simvastatin treatment group (41%), $P<0.01$, as well as a nonsignificant incidence of cardiovascular events.¹

A significant amount of discussion has been generated based on these results. Some think that the ezetimibe was not enough of an additional treatment for HeFH patients, since they have such a high baseline LDL level compared to an average patient with hyperlipidemia. Another consideration is that, in general, the primary endpoint of IMT is not currently the best objective data for heart disease. LDL is the current gold standard, and IMT is used more as a measure for atherosclerotic disease.³

The Food and Drug Administration (FDA), American College of Cardiology (ACC), and the American Heart Association (AHA) have all issued statements regarding the ENHANCE Trial. The ACC states that no significant clinical judgments can be made based on this study by itself, and patients should not stop taking their medication without discussing it with their prescriber.⁴ The AHA states that the study was too small and patients were not evaluated for a long enough time to determine a reduction in clinical outcomes, such as myocardial infarction or death. They recommend further investigation to evaluate ezetimibe.⁵ The FDA has not come to a conclusion about the implications of the ENHANCE study, but does not recommend health care providers discontinue using these medicines. Merck-Schering-Plough is preparing a complete report on this study, and it will require an additional 6 months for the FDA to completely review the data before any decisions will be made.⁶

At this time, it would be considered prudent to continue following current guidelines. Patients should be educated that the ezetimibe/simvastatin combination is not dangerous but further investigation is underway to determine the context of these results.³ Further comparative data between simvastatin and ezetimibe/simvastatin are expected to be reported at the American College of Cardiology meeting in March 2008, and may offer additional clarity to this topic.

Vytorin and Zocor: The ENHANCE Trial	1
New FDA warnings on bisphosphonates	2
Increased bleeding risk with SSRIs & NSAIDs	2
FDA actions against bio-identical hormones	3
News Clips	3

References:

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New FDA Warnings on Bisphosphonates by Andy Meyer

On January 17, 2008, the FDA released new warnings regarding severe bone, joint, and/or muscle pain in patients receiving bisphosphonate therapy. Pain has been reported as a side effect in prescribing information, but bisphosphonates may be overlooked as the etiologic agent. Current bisphosphonates on the market include Actonel (risendronate), Actonel (risendronate)+ Ca, Aredia (pamidronate), Boniva (ibandronate), Didronel (etidronate), Fosamax (alendronate), Fosamax (alendronate)+ D, Reclast (zoledronic acid), Skelid (tiludronate), and Zometa (zoledronic acid). Bisphosphonates are used to treat hypercalcemia of malignancy, Paget's disease, bone metastases from solid tumors, and most commonly to prevent and treat osteoporosis¹.

Severe musculoskeletal pain may begin within days, months, or years of beginning therapy. Risk factors and incidence of this adverse event are currently unknown. Pain was reported in clinical trials of all bisphosphonates, but the severity has not been documented. This pain is different from the acute phase response to initiating bisphosphonate therapy. The acute phase response is characterized by fever, chills, bone pain, myalgia, and arthralgia that can accompany initial treatment, and usually resolves with continued use of the medication. In 2005, a case review of bone, joint, and/or serious muscle pain in patients taking alendronate and risedronate was published. Pain was not limited to an anatomical site, the mean time to onset was 91 days (1 day – 52 months), and was described as extreme, debilitating, and incapacitating. The pain was treated with a variety of analgesics and in some cases, the discontinuation of the bisphosphonate. Some patients experienced immediate relief after withdrawal, while others had extended time before relief, or incomplete relief².

The FDA has published recommendations regarding bisphosphonates in patients with severe musculoskeletal pain¹. Healthcare providers should consider bisphosphonates as a possible cause of the pain. If severe symptoms occur, discontinuation of therapy should be considered. Pain symptoms should be monitored for duration, quality, and severity while on therapy and after withdrawal of treatment. As always, the risks and benefits of bisphosphonate therapy should be evaluated on a case-by-case basis.

References:

1. Information for Healthcare Professionals: Bisphosphonates. U.S. Food and Drug Administration. <http://www.fda.gov/cder/drug/InfoSheets/HCP/bisphosphonatesHCP.htm>
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Recent FDA Action Against Compounded Bio-Identical Hormone Replacement Therapy by Christina Trachte

In January 2008, the Food and Drug Administration (FDA) issued warnings to several pharmacy compounding locations that claims of safety and efficacy for their compounded "bio-identical hormone replacement therapy" (BHRT) are false and misleading, and therefore, in violation of federal law. These compounding sites have made false claims that BHRT compounds are superior to already existing FDA-approved hormone replacement therapy formulations and that BHRT formulations can treat various conditions, such as cancer, stroke and Alzheimer's disease. The compounded BHRT formulations made by these operations use combinations of estriol, as well as estrogen and progesterone. Estriol is not FDA-approved. The FDA is concerned that women are being misled into using these compounded BHRT formulations, which have not been studied and may be contaminated or ineffective.

Prior to the FDA's warnings, the American College of Obstetricians and Gynecologists (ACOG) issued a statement in October 2005, recommending that compounded bio-identical hormones should be considered to have all of the risks of FDA-approved hormone treatments and additional possible risks, such as lack of purity, safety and efficacy.²

If the pharmacy compounding sites responsible for the false and misleading claims do not comply with FDA requirements, the FDA may take action to stop production and seize compounded BHRT. However, these FDA warnings do not apply to pharmacy operations which are following pharmacy compounding practice laws and avoiding false or misleading claims. Pharmacies may compound formulations for an individual patient with a physician's prescription if the exact formulation needed is not available commercially.¹

Prior to issuing official warning letters to the pharmacy compounding sites involved in the false and misleading statements, the FDA received approximately 70,000 comments, both positive and negative, from citizens, consumer groups, health care providers, pharmacy compounding sites and other groups concerned about BHRT compounding.³ If patients experience problems with compounded BHRT, it is recommended for the physician and/or patient to submit a MedWatch report at www.fda.gov/medwatch or call 1-800-FDA-1088.¹

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Increased Risk of Gastrointestinal Bleeding in Patients Using SSRIs and NSAIDs by Brian Murray

A recent meta-analysis in the journal, *Alimentary Pharmacology and Therapeutics*, has brought attention to an increased risk of upper gastrointestinal bleeding (UGIH) caused by concomitant use of Selective Serotonin Reuptake Inhibitors (SSRIs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including COX-2 inhibitors. The article, authored by Loke and colleagues, compiles data from three case-controlled studies and one cohort study and included a total of 153,000 patients.

The first case-controlled study looked at records from the United Kingdom General Practice Research Database from the years 1993-1997. It included patients between the ages of 40 to 79, and it had age, sex, and year-matched controls. The second case-controlled study used records from the Health Improvement Network in England and Wales. This case-controlled study also had age, sex, and time-matched controls. The third case-controlled study looked at medical records from Finland. It excluded patients with a previous GI bleed in the past four years and patients receiving institutional care. It also had age, sex, and time-matched controls. The cohort study took place in Denmark and used records from the Prescription Database and Hospital Discharge Register from the years 1991 to 1995. It included any patients who did not have a risk factor for GI bleeding and had received a prescription for antidepressants.

Although product information from the manufacturers include gastrointestinal bleeding as an adverse effect, details concerning severity or frequency of these occurrences are not available. The researchers aimed to quantify the UGIH caused by SSRIs, as well as investigate whether NSAIDs may further increase this risk.

The mechanism by which SSRIs increase the risk of GI bleeding is thought to be caused by a block in the reuptake of serotonin into platelets. Platelets need serotonin for proper aggregation and other hemostatic function. Depleted serotonin levels may hinder platelet aggregation, and moreover, increase GI bleeds.

The data from this observational study shows a statistically significant increase in UGIH in patients on SSRI therapy. The increase is even greater for patients on concomitant SSRI and NSAID therapy. Based on the results of this meta-analysis, the number-needed-to-harm (NNH) for patients aged 50 or above taking SSRIs with no UGIH risk factors was 411 per year. With concomitant NSAID and SSRI use in this population, the NNH dropped to 106.

Some of the data analyzed in this meta-analysis did include Cox-2 inhibitors, although because data included were a result of combining four different studies, it is difficult to ascertain the exact impact of traditional versus selective NSAIDs. Two of the four observational studies included in the meta-analysis specifically mentioned the inclusion of Cox-2 selective inhibitors in the data analysis, while the other two studies did not identify the type of NSAID included in the analysis. In the two studies which mentioned Cox-2 inhibitors, the data appear mixed with one study showing a significantly greater risk of serious upper GI event with non-selective versus Cox-2 selective NSAIDs, and the other showing similar rates of GI bleeding. Unfortunately, the other analyzed data, including the meta-analysis, do not offer greater detail on the relationship between NSAID type and risk of SSRI interaction resulting in GI events. Post-marketing reports submitted to Canadian and U.S. officials showed that approximately 1/3 of upper GI bleeds associated with the concomitant use of NSAIDs and SSRIs were in patients taking Cox-2 inhibitors.

Since this was an observational study and not a randomized controlled trial, the data do have limitations. For instance, the severity of each UGIH was not specifically mentioned. The study therefore includes a population with varying levels of upper GI bleeding. However, the data suggest that SSRIs, along with NSAID use, can potentially increase the risk of gastrointestinal bleeding. It does not specify which SSRIs or NSAIDs pose the largest risk, but it does encourage thought on whether to treat patients with a combination of these medications.

Reference: Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Alim Pharmacol Ther* 2008; 27(1): 31-40.

News Clips



- There is increasing evidence in the form of case reports of varenicline (Chantix®) being linked with neuropsychiatric side effects, including agitation, depression, and suicide. The FDA has asked Pfizer to display more prominent warnings about this, and is working with Pfizer to produce a medication guide for patients. The FDA is still evaluating post-marketing case reports of Chantix® regarding psychiatric side effects. Further information on this new warning will be included in the next edition of *Health Matters*.
- The FDA has approved the first generic equivalent for Fosamax. Shipments to pharmacies are expected to begin immediately.

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