

FUTURA/OASIS-8 Solves Fondaparinux Paradox

BY BRUCE JANCIN

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STOCKHOLM – The use of fondaparinux as an antithrombotic agent in percutaneous coronary intervention for acute coronary syndromes could get a major boost in clinical practice now that the optimal dose of adjunctive unfractionated heparin has been carefully de-

termined in the large randomized FUTURA/OASIS-8 study.

It's clear from the study that standard-dose unfractionated heparin, not low-dose, is the right way to go for PCI in ACS patients treated with fondaparinux, Dr. Sanjit S. Jolly said at the congress.

Many interventional cardiologists have balked at using fondaparinux, a synthetic factor Xa inhibitor, despite its impressive performance in the earlier Organi-

zation to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, in which it halved major bleeding and produced a 17% reduction in mortality compared with enoxaparin (N. Engl. J. Med. 2006;354:1464-76).

The concern among interventionalists has been that catheter thrombosis rates were higher with fondaparinux in OASIS-5. Although adjunctive unfractionated heparin will prevent that prob-

lem, the optimal dose of heparin needed to avoid catheter thrombosis and ischemic complications without compromising fondaparinux's low rate of major bleeding has been unclear – until FUTURA/OASIS-8, said Dr. Jolly of McMaster University, Hamilton, Ont.

The Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA)/OASIS-8 trial was a double-blind, randomized study involving 2,026 patients undergoing PCI within the next 72 hours for high-risk ACS at 179 hospitals in 18 countries. All patients received 2.5 mg of fondaparinux subcutaneously once daily; after entering the catheterization lab, they were randomized to adjunctive standard- or low-dose unfractionated heparin. Standard-dose heparin was defined as 60 U/kg in the event a glycoprotein IIb/IIIa inhibitor was used and 85 U/kg if not, with dosing guided by activated clotting time (ACT). Low-dose heparin was given at 50 U/kg regardless of glycoprotein IIb/IIIa inhibitor therapy, and without ACT measurement.

The primary end point, major or minor bleeding or major vascular access-site complications within 48 hours after PCI, occurred in roughly 5% of both study arms. But there was a nominally significant difference between the two treatment groups in the key secondary end point: periprocedural major bleeding and the 30-day rate of death, MI, or target vessel revascularization. This occurred in 3.9% of the standard-dose unfractionated heparin group, vs. 5.8% of those on low-dose heparin, representing a 51% increased risk with low-dose therapy.

The risk of major bleeding within 48 hours was 1.1% in the standard-dose unfractionated heparin arm and 1.2% with low-dose heparin in FUTURA/OASIS-8, vs. 3.6% with enoxaparin in OASIS-5, he noted.

"FUTURA/OASIS-8 will definitely improve uptake in the community and amongst interventional cardiologists," he said.

Dr. Ralph Brindis, American College of Cardiology president, agreed.

"This could be a paradigm change," he predicted in an interview.

"We have been very leery, at least in the United States, in utilizing fondaparinux in ACS patients we're going to take to the cath lab, despite the incredible benefits shown in OASIS-5. ... But they've shown in FUTURA/OASIS-8 that you can do so safely and effectively. I think this is going to be very helpful in the cath lab," added Dr. Brindis, an interventional cardiologist and senior advisor for cardiovascular disease at Northern California Kaiser Permanente in Oakland.

Simultaneously with the Stockholm presentation, the study results were published online (JAMA 2010 Aug. 31 [doi:10.1001/jama.2010.1320]).

Disclosures: Dr. Jolly received honoraria and research grants from GlaxoSmithKline, the trial sponsor. Dr. Brindis said he had no financial conflicts.

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 261 (25%) had baseline fasting serum TG levels between 200 and 300 mg/dL, 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL; the median post-treatment fasting TG was 195 mg/dL in the WELCHOL group and 177 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 5% (p=0.22), 22% (p<0.001), and 18% (p<0.001) when added to metformin, insulin and sulfonylureas, respectively [See Warnings and Precautions (5.2) and Clinical Studies (14.2) in the full prescribing information]. In comparison, WELCHOL resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial [See Clinical Studies (14.1) in the full prescribing information].

Treatment-emergent fasting TG concentrations \geq 500 mg/dL occurred in 4.1% of WELCHOL-treated patients compared to 2.0% of placebo-treated patients. Among these patients, the TG concentrations with WELCHOL (median 604 mg/dL; interquartile range 538-712 mg/dL) were similar to that observed with placebo (median 644 mg/dL; interquartile range 574-724 mg/dL). Two (0.4%) patients on WELCHOL and 2 (0.4%) patients on placebo developed TG elevations \geq 1000 mg/dL. In all WELCHOL clinical trials, including studies in patients with type 2 diabetes and patients with primary hyperlipidemia, there were no reported cases of acute pancreatitis associated with hypertriglyceridemia. It is unknown whether patients with more uncontrolled, baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL [See Contraindications (4) and Warnings and Precautions (5.2)].

Cardiovascular adverse events: During the diabetes clinical trials, the incidence of patients with treatment-emergent serious adverse events involving the cardiovascular system was 3% (17/566) in the WELCHOL group and 2% (10/562) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

Hypoglycemia: Adverse events of hypoglycemia were reported based on the clinical judgment of the blinded investigators and did not require confirmation with fingerstick glucose testing. The overall reported incidence of hypoglycemia was 3.0% in patients treated with WELCHOL and 2.3% in patients treated with placebo. No WELCHOL treated patients developed severe hypoglycemia.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of WELCHOL. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during WELCHOL initiation then periodically thereafter.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Thyroid hormone replacement should be administered 4 hours prior to WELCHOL [See Drug Interactions (7)].

Gastrointestinal Adverse Reactions

Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

Laboratory Abnormalities

Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding or *in vivo* drug interaction studies with colestevlam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colestevlam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug.

Table 4
Drugs Tested in *In Vitro* Binding or *In Vivo* Drug Interaction Testing or With Post-Marketing Reports

Drugs with a known interaction with colestevlam ^a	cyclosporine ^c , glyburide ^a , levothyroxine ^a , and oral contraceptives containing ethinyl estradiol and norethindrone
Drugs with postmarketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin ^a , warfarin ^b
Drugs that do not interact with colestevlam based on <i>in vitro</i> or <i>in vivo</i> testing	cephalexin, ciprofloxacin, digoxin, warfarin ^b , fenofibrate, lovastatin, metformin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

^a Should be administered at least 4 hours prior to WELCHOL

^b No significant alteration of warfarin drug levels with warfarin and WELCHOL coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). [See Post-marketing Experience (6.2)]

^c Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL.

In an *in vivo* drug interaction study, WELCHOL and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of WELCHOL and warfarin coadministration on INR. In postmarketing reports, concomitant use of WELCHOL and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating WELCHOL and frequently enough during early WELCHOL therapy to ensure that no significant alteration in INR occurs. Once the INR is stable, continue to monitor the INR at intervals usually recommended for patients on warfarin. [See Post-marketing Experience (6.2)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of colestevlam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm. Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colestevlam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colestevlam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colestevlam hydrochloride is not expected to be excreted in human milk because colestevlam hydrochloride is not absorbed systemically from the gastrointestinal tract.

8.4 Pediatric Use

The safety and effectiveness of WELCHOL as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH [See Clinical Studies (14.1) in the full prescribing information]. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo [See Adverse Reactions (6.1)].

Due to tablet size, WELCHOL for Oral Suspension is recommended for use in the pediatric population. Dose adjustments are not required when WELCHOL is administered to children 10 to 17 years of age. WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia: Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were \geq 65 years old, and 58 (4%) were \geq 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 249 (22%) were \geq 65 years old, and 12 (1%) were \geq 75 years old. In these trials, WELCHOL 3.8 g/day or placebo was added onto background anti-diabetic therapy. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No special considerations or dosage adjustments are recommended when WELCHOL is administered to patients with hepatic impairment.

8.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] 50-80 mL/min), 53 (5%) had moderate renal insufficiency (CrCl 30-50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with CrCl <50 mL/min (n=53) and those with a CrCl \geq 50 mL/min (n=1075).

10 OVERDOSAGE

Doses of WELCHOL in excess of 4.5 g/day have not been tested. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more severe local gastrointestinal effects (e.g., constipation) than recommended doses.

Welchol
(colesevelam HCl)

Marketed by:

Daiichi Sankyo, Inc.
Parsippany, New Jersey
07054

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