

Nesiritide — Not Verified

TO THE EDITOR: In his Perspective article, Topol (July 14 issue)¹ discusses current clinical practice with respect to nesiritide. According to the Food, Drug, and Cosmetic Act, drug approval can be withdrawn when “new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, *shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved* (emphasis added).”²

Both of the Food and Drug Administration (FDA) reviews, in 1999³ and 2001,⁴ omitted mortality analyses such as the one we recently published,⁵ and the results of PROACTION (the Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Nesiritide) were not available at the time of those reviews. Both fulfill the definition of new evidence, according to the FDA in its recent decision to withdraw enrofloxacin.⁶ Moreover, the FDA decision letter in the enrofloxacin case makes it clear that if there is “a reasonable basis from which serious questions may be inferred about the ultimate safety of [a drug] . . . the drug’s sponsor has the burden of persuasion on the ultimate question of whether [a drug] is shown to be safe.”⁶

Our recent pooled analyses included all three randomized, double-blind, controlled clinical trials of nesiritide in patients with acute decompensated heart failure who had dyspnea at rest or on minimal exertion — the current FDA indication — and estimated that the risk of death within 30 days was 74 to 86 percent higher after the use of nesiritide than after the use of control medication, with P values ranging from 0.04 to 0.06 among the analyses.⁵ Although these analyses do not provide proof, by providing a reasonable basis for concern about the safety of nesiritide, Scios (the developer and marketer of nesiritide) shares the same burden of proof that was faced by the sponsor of enrofloxacin: the need to demonstrate that the drug is safe in the intended population.

Although controlled trials demonstrate that nesiritide reduces symptoms of dyspnea and lowers pulmonary-capillary wedge pressure, no clinical trial has demonstrated that nesiritide is safe in pa-

tients with acute decompensated heart failure who have dyspnea at rest or on minimal exertion. To be consistent with federal regulations addressing the basis for drug withdrawal,² the FDA can and should withdraw approval for the marketing of nesiritide. At a minimum, an advisory panel to the FDA should address these issues in a public forum.

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TO THE EDITOR: Scios disagrees with Topol’s perspective on nesiritide for the treatment of acute decompensated heart failure. His conclusion depends on numerous inaccuracies relating to the Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC) trial. In the VMAC trial, 81 percent (not 30 percent) of patients received diuretics before enrollment. The lack of prescribed dose titration of nitroglycerin was criticized, but regulatory requirements dictate dosing as labeled in pivotal trials. Also, a balanced assessment of the safety of nesiritide should have included the recent large observational study on vasoactive drugs in acute decompensated heart failure.¹

No medicine for acute decompensated heart failure has ever been found to offer a survival benefit in controlled trials. Medications other than nesiritide are used off label, improve only surrogate end points, have significant toxic effects,^{1,2} or are associated with tachyphylaxis.³

With its current and planned research activities and the Acute Decompensated Heart Failure National Registry, Scios, the developer and marketer of nesiritide (Natreacor), is committed to evidence-based medicine. Nesiritide is the only treatment for acute decompensated heart failure that has been proved in controlled clinical trials to provide a clinical benefit—improvement of dyspnea, which is not a surrogate end point. Safe and effective when used as labeled, nesiritide continues to be an important therapy for acute decompensated heart failure.

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TO THE EDITOR: Topol's Perspective article touches on a pharmaceutical manufacturer's invitation to practitioners to earn money from office-administered medication and the evident overuse of the medication in question—in this case, of a medication of little benefit.

In rheumatology, we have a situation in which the manufacturer of infliximab (Remicade) provided information to enable physicians to earn money by office infusions of this drug, which is effective for rheumatoid arthritis but not more effective than two other drugs that may be injected at home by patients and from which the physician derives no income. The current president of the American College of Rheumatology and at least one past president encourage this as a way to offset poor reimbursement for patient care. Medicare policy is also skewed toward the use of the infusions by paying for them and the drug used and by denying payment for home use of the alternative drugs. It has also come to my attention that the infusions are being given to patients who do not have the recognized indications.

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DR. TOPOL REPLIES: The medical community is indebted to Drs. Sackner-Bernstein and Aaronson, who published the pooled analyses of randomized, placebo-controlled trials of nesiritide that demonstrate an 80 percent increase in mortality¹ and a 50 percent increase in renal dysfunction.² Beyond the serious questions about nesiritide safety, there have been no trials to demonstrate clinically meaningful efficacy. This would require a reduction of death or repeated hospitalization for heart failure at 30 days, and such a trial has not been initiated, despite the drug having been approved more than 4 years ago. Clearly, the minimal criteria for safety and efficacy have not been fulfilled, and I agree that drug withdrawal, until such time validation is assured, is a reasonable proposition.

Dr. Schreiner raises several points, each of which can be readily addressed. In the FDA advisory committee review in May 2001, the VMAC trial was discussed in depth. An expert panelist was concerned about withholding diuretic therapy in the trial and pointed out that “only 30 percent of the Natreacor patients got an intravenous diuretic within 6 hours before they began these [study drug] infusions.” The principal investigator of the trial responded, “You hit right smack dab on an incredibly important thing.”³ The trial was not blinded for half the patients in the trial who had a pulmonary artery catheter in place. Nitroglycerin was essentially not titrated, with a mean dose of only 29 μ g per minute in noncatheterized patients and 42 μ g per minute in catheterized patients.⁴ Nevertheless, the significant excess in length of hospital stay with nesiritide as compared with nitroglycerin (10.0 vs. 8.1 days, $P=0.008$) was not reported even in the primary article.⁵

Observational studies are not an adequate or appropriate substitute for randomized trials. Furosemide, nitroglycerin, and nitroprusside are standard, inexpensive medications that have been used in this setting for decades and that have not been associated with an excess risk of death or kidney damage. Furthermore, the short half-life of nitroglycerin is more protective against clinically significant hypotension, which is yet another untoward effect of nesiritide. The statement that “Scios is committed to evidence-based medicine” is not in agreement with its failure to conduct a definitive randomized trial or its promotion of outpatient infusion “tune-up” centers across the country, for which there are no data to justify.

Dr. April raises awareness about the problems of reimbursement to physicians for administration of infliximab. Both the situation with this medication and the situation with nesiritide serve as examples of what may occur when there is alignment of financial incentives for manufacturers and physicians.

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Torcetrapib and Atorvastatin

TO THE EDITOR: Avorn's proposal in his Perspective article (June 23 issue)¹ that the combination of torcetrapib and atorvastatin is market-driven, undermining its usefulness, is baseless. The program does not extend the patent on atorvastatin. Its basic aim is to provide efficiently the greatest medical benefit to the most patients while maintaining the greatest likelihood of success.

Mandatory control of low-density lipoprotein (LDL) cholesterol is a foundation of treatment for patients who are at increased risk for heart disease, including those with isolated low levels of high-density lipoprotein (HDL) cholesterol.² Torcetrapib alone at the dose used in phase 3 studies does not provide sufficient reduction of the LDL cholesterol level. Therefore, researchers cannot ethically study torcetrapib alone. Combining it with atorvastatin, a safe and effective statin,³ will provide the needed control of LDL cholesterol.

Early clinical data from a phase 2 study showed that torcetrapib alone causes highly variable changes in LDL cholesterol levels, including notable increases, in patients with triglyceride levels of 150 mg per deciliter (1.69 mmol per liter) or higher. Combining torcetrapib with atorvastatin eliminated this variance, implying that robust lowering of triglyceride levels is an important component of treatment. Pfizer saw this finding as reinforcing the need for atorvastatin as the concurrent treatment, given its triglyceride-lowering advantage over other statins.⁴

The hypothesis that torcetrapib-atorvastatin will ultimately benefit patients by raising HDL cholesterol levels and incrementally lowering LDL cholesterol levels remains to be proven. The regulatory

hurdles for approval are clear: unambiguous demonstration of an efficacy benefit over atorvastatin alone, including lipid and vascular benefits, along with documentation of safety.⁵ Recognition of these hurdles solidified the need to use a single statin in the initial development program. It allows valid hypothesis testing by keeping the statin effect constant. The "all comers" approach that has been suggested opens trial results to important potential biases and ambiguities, since all the marketed statins have different efficacy and safety profiles. Regulatory approval requires unambiguous results. The single torcetrapib-atorvastatin product will also enhance long-term patient compliance and affordability.⁶ Avorn's concern about high cost is without merit. We do not yet have a clinical profile to inform pricing.

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