we could rarely choose one member of a drug class over another in order to reduce the risk of adverse interactions. But for many drug classes, including the statins, we do have sufficient information to choose members of the class that will reduce the drug interaction risk in specific patients. To blur these differences is to put patients at greater risk of a preventable adverse outcome.

Philip Hansten, PharmD
School of Pharmacy
University of Washington
Seattle, Washington 98195-7630
E-mail: hansten@u.washington.edu
doi:10.1016/S0735-1097(03)00637-5

REFERENCES


Efficacy of Simvastatin and Ezetimibe in Treating Hypercholesterolemia

In a recent editorial published in JACC, Dr. Sacks summarized the efficacy of co-administration of simvastatin and ezetimibe, a novel cholesterol absorption inhibitor with a mechanism of action that is complementary to statins (1,2). I appreciate the opportunity to provide some additional data, likely not available at the time Dr. Sacks drafted his editorial, to clarify some of the estimates provided by Dr. Sacks (2).

Dr. Sacks took a hypothetical patient, with a pretreatment low density lipoprotein cholesterol (LDL-C) level of 190 mg/dl, and calculated LDL-C reductions and relative risk reduction (RRR) estimates for simvastatin alone and simvastatin/ezetimibe co-administration. It should be pointed out that the calculated LDL reductions and RRR estimates for simvastatin alone and simvastatin/ezetimibe in the editorial are actually too low and underestimate the benefit of using ezetimibe with a statin compared to a statin alone. This is due to the iterative use of the estimated 6% reduction of LDL-C per doubling of simvastatin relative to LDL-C values that were already reduced by simvastatin treatment. The “6% rule” for incremental LDL-C lowering with doubling of statin dose applies to the estimated reduction calculated relative to the pre-statin LDL-C baseline (in this case, 190 mg/dl). The correct sequence of values, therefore, would be as follows: 20 mg simvastatin results in LDL-C of 125 mg/dl (34% reduction from the base of 190 mg/dl); 40 mg simvastatin results in LDL-C of 114 mg/dl (40% reduction from 190 mg/dl); and 80 mg simvastatin results in LDL-C of 102 mg/dl (46% reduction from 190 mg/dl). The RRR values would similarly decrease.

The same issue applies with respect to the calculation of anticipated incremental lowering based on addition of ezetimibe. Assuming a 14% reduction with ezetimibe, when ezetimibe is added to the hypothetical patient already on 20 mg of simvastatin with an LDL-C of 125 mg/dl, the reduction of LDL-C by 14% (of 190, not 125 mg/dl) would result in a further decrease in LDL-C of 26.6 mg/dl, bringing the patient to below the goal of <100 mg/dl without additional simvastatin titration.

The estimated efficacy from the above analysis is highly consistent with the reported 27% reduction in LDL-C relative to baseline (24% relative to placebo) observed when ezetimibe was added to ongoing simvastatin therapy (3). The data from the clinical trials of initiation of ezetimibe with both simvastatin and atorvastatin indicate that 10 mg of ezetimibe added to either statin produces incremental LDL-C lowering similar to that produced by 80 mg of the corresponding statin, an additional reduction that would require an 8-fold increase in statin dosage to be achieved by titration (4).

Dr. Sacks makes clearly important points about balancing benefit and potential harm, including the fact that statin-related adverse effects are dose dependent and occur more commonly at the highest doses (5). Although the long-term safety experience...
with ezetimibe is more limited, the profile to date is very encouraging, particularly with respect to the lack of any incremental risk with respect to the most worrisome statin-related side effects, namely myopathy and rhabdomyolysis. Thus, considering the large numbers of patients not at NCEP ATP III therapeutic goals as well as the well-recognized reluctance of many physicians to titrate, I believe that co-administration of ezetimibe with low-dose statins provides a valuable new option for treatment of hypercholesterolemia.

Michael H. Davidson, MD, FACC
Rush-Presbyterian–St. Luke’s Medical Center
Chicago Center for Clinical Research
515 North State Street
Suite 2700
Chicago, Illinois 60610
E-mail: mdavidson@protocare.com
doi:10.1016/S0735-1097(03)00638-7

REFERENCES

REPLY
I thank Dr. Davidson for clarifying some of the estimates for low density lipoprotein (LDL) reduction that I computed for statin and ezetimibe doses (1). Although we do have treatment goals for LDL cholesterol (LDL-C), it is worth emphasizing that it is risk reduction that is the ultimate goal. The additional risk reduction expected from two doublings of a statin dose or from ezetimibe remains modest in typical patients, about 15% for a patient with a pretreatment LDL-C of 190 mg/dl, and 12% when the pretreatment LDL-C is 140 mg/dl. This reflects the modest efficacy of ezetimibe, a 14% lowering of LDL-C shown in Dr. Davidson’s excellent study (2), and of two doublings of statin doses. This magnitude is consistent with much of the literature on the drug. The added value in terms of risk reduction appears rather modest and needs to be balanced against the cost, lack of long-term outcome data, and need for other medications, particularly in older patients.

My perspective is that the benefits and safety of statin therapy are very well established, and I favor its use across the approved dose ranges. I am finding ezetimibe useful in combination with 40 mg or 80 mg of a statin in patients with moderate to severe hypercholesterolemia for whom more substantial risk reduction should occur from additional LDL reduction. I am much less convinced that adverse effects of statin therapy truly occur in more than a very few patients. I base this on results of trials that compare adverse effects reported during statin therapy with those during placebo treatment in tens of thousands of patients (3,4). Myalgia is a common feature of the human condition, inexorably increasing with aging. When patients complain of myalgias while taking statins, it is important to ensure that it fits the clinical features of statin-myopathy, following the accepted guidelines for this diagnosis (5). Whether ezetimibe or other nonstatin LDL-lowering drugs like colesevelam offer a useful alternative in "statin intolerant" patients remains to be determined.

Frank M. Sacks, MD
Harvard School of Public Health
Department of Nutrition
665 Huntington Ave.
Boston, Massachusetts
E-mail: fsacks@hsph.harvard.edu
doi:10.1016/S0735-1097(03)00639-9

REFERENCES