EDITORIAL

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Did Niacin Get a Bum Rap?

I had thought that my long-standing romance with niacin was finally over. Although it was a very early love of mine, reluctantly I had gone along with the mainstream consensus. It seemed that niacin had been sent into near-permanent pharmaceutical exile by the devastating one-two punches of the AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) and the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) studies. I had even stopped taking my own self-prescribed niacin 2,500 mg twice a day, which I had been religiously consuming for over 2 decades. But before long, I found that I had real difficulty divorcing myself completely from the charms of this lipid-lowering Lorelei. Now, after agonizing over the issue for some time, I'm here to tell you that niacin almost certainly did get a bum rap and should be restored as an important tool in your therapeutic armamentarium.

A recent report that niacin seems to function partially as an inhibitor of the PCSK-9 enzyme accelerated my reconsideration. The inhibition of PCSK-9, an enzyme that removes low-density lipoprotein cholesterol (LDL-C) receptors from hepatocytes, is the hot new way of dropping LDL-C levels. And I mean *really* dropping LDL-C levels. Studies conducted with investigational compounds developed by Amgen and Pfizer have shown truly dramatic drops in LDL-C levels by as much as 80%—often down to ridiculously low levels (around 25 mg/dL).

Of course, we are still waiting for outcome trials, which will answer the critical question: Are these dramatic falls in LDL-C levels actually associated with meaningful reductions in the occurrence rates for cardiovascular events such as myocardial infarction and stroke? For now, inhibiting PCSK-9 seems to be a good way to change the lipid profile dramatically. Even if niacin is not nearly as potent an inhibitor of the PCSK-9 enzymes as some newer compounds, the fact that it has measurable inhibiting activity seems enough to earn it a second look.

The concerns over niacin derive almost entirely from the results of the AIM HIGH study and the HPS2-THRIVE trials. Thus, any effort to rehabilitate niacin will require a reckoning with each of these major trials.

I was one of the original AIM HIGH investigators, but our study site at the Phoenix VA eventually was removed from the trial because of poor enrollment. Nonetheless, I had a front-row seat to observe the conduct of the trial, and it seemed less than optimal. The relatively infrequent monitor visits for this study probably contributed to the finding that the lipid differences between the 2 study groups were considerably smaller than they could have been. It was my impression that study sites did not have their feet held to the fire when niacin compliance became problematic for subjects randomized to the larger dose of niacin.

The study design also contributed to blunting the difference between the 2 study groups. Subjects in the control group actually received 200 mg of immediate-release niacin to help blind the study by ensuring that all subjects experienced a niacin flush. The statin dose wound up being higher in the control group, and the use of the add-on lipid-lowering agent ezetimibe was also greater (22% vs 10%) in the control group. All these factors would tend to blunt the differences between the 2 groups, and indeed lipid levels did improve significantly in both groups.

To add insult to injury, the trial was stopped after just 3 years. A number of other lipid trials that were ultimately positive had not yet reached a statistically significant separation between the control and the experimental groups after that relatively brief study interval. Although these study flaws are hardly fatal, when taken together, they suggest the need to maintain an open mind. If niacin is like Brylcreem and "a little dab'll do ya," then the small dusting received by the control subjects might have been cardioprotective enough to blunt any differences in event rates between the 2 groups, especially over the truncated period of the actual trial.

What about the much larger HPS2-THRIVE study; surely there can't be similar flaws in that study as well? Well, a critical review identifies a number of significant shortcomings. Although conducted by British academics through the Medical Research Council, the trial was funded and largely designed by Merck, which had hoped it would demonstrate the clinical utility of its new combination of extended-release niacin and an anti-flushing agent called laropiprant, a prostaglandin-inhibiting compound. One has only to remember the fiasco with the cyclo-oxygenase-2 inhibitor celecoxib to recognize the potential

increase in cardiovascular events of any agent that blocks prostaglandins. Any failure of the niacin/laropiprant arm to show a reduced cardiovascular event rate on top of baseline statin therapy might have been because the laropiprant was increasing events enough to cancel any reductions the niacin might have produced.

A fair trial of the potential effectiveness of a niacin preparation on top of statin therapy should test niacin in a clinical setting in which it is typically prescribed. I'm not going far out on a limb by asserting that the majority of niacin prescriptions are written for patients who have low levels of high-density lipoprotein cholesterol (HDL-C), typically < 40 mg/dL but often much lower than that. Yet the mean HDL-C in the HPS2-THRIVE study was a robust 44 mg/dL, and the mean LDL-C level was a well-controlled 63 mg/dL. The subjects who were randomized to receive either placebo or niacin/laropiprant on top of their preexisting statin therapy were simply not the typical patients who would normally be started on niacin.

The supposedly airtight case against niacin isn't really so strong after all. Where does this leave us? Let's not forget that there is a sizable population of individuals who cannot or will not take statins. Surely these individuals would be better off on niacin therapy than on no therapy, particularly if they have a combination of low HDL-C levels, elevated triglyceride levels, and elevated LDL-C levels.

I currently prescribe this combination in patients who have persistently elevated triglyceride levels even after their statins have been maxed out, because I believe that lowering triglycerides in such patients may well translate into lower cardiovascular risk. Some recent evidence suggests that the epidemiologic association of low HDL-C levels with cardiovascular events may not be due so much to the low HDL-C levels per se, but rather to the very frequent association of elevated triglyceride levels—the true culprit, with low HDL-C levels. So if you have a need to lower either triglyceride levels or LDL-C levels in a patient already taking as much statin as they can tolerate, niacin would be a very reasonable drug to consider. My romance with niacin has been rekindled, and perhaps you'll want to give it a second look as well. ●

Author disclosures

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