

MEETING REPORT

Targeting two sources of cholesterol

Physicians need to target both sources of cholesterol in order to achieve the increasingly stringent lipid levels being set by international guidelines, a recent meeting was told. The meeting on the management of hyperlipidaemia, held in Galway recently to mark the launch of INEGY®, a new combination therapy of ezetimibe and simvastatin, heard that therapeutic goals for hyperlipidaemia are likely to become even more challenging in the near future.

Chairing the meeting, Dr Fidelma Dunne, consultant endocrinologist, University College Hospital, Galway, said emerging data suggest that target total cholesterol and low density lipoprotein (LDL) levels will become lower than are currently accepted.

At present, the management of hyperlipidaemia aims for total cholesterol <5mmol/l and LDL <2.6mmol/l.¹ Triglycerides and high density lipoprotein (HDL) cholesterol are also increasingly important, she said, and the management of the entire lipid profile is now seen as vital to the overall reduction of cardiac risk.¹

“We are all aware that there is substantial evidence to support the treatment of hyperlipidaemia^{2,3} in the secondary prevention of cardiovascular disease [CVD] and, more recently, in terms of primary prevention in patients with diabetes,” said Dr Dunne.^{4,5}

Dr Dunne cited a number of studies demonstrating the importance of LDL reduction in the secondary prevention of CVD.^{2,3} She pointed out that the CARE study has also supported targeting total cholesterol levels in secondary prevention and, more recently, the CARDS study has highlighted the role of reducing LDL in the primary prevention of CVD.^{4,5}

“Despite international guidelines and a host of effective therapeutic options, we are still failing in achieving target lipid levels”, Dr Dunne added.

Dr Neil Boyle, medical director, Merck Sharp & Dohme Ireland (Human Health) Ltd, cited data which supported Dr Dunne’s view. Dr Boyle reported that a recent review of the management of at-risk primary care patients in the UK revealed that <15% of patients with established coronary heart disease (CHD) were being treated to target.⁶

The study, published in 2004 in the *British Journal of Cardiology*, examined 78,600 patients with a diagnosis of CHD. It was discovered that just 48% of these patients had a valid cholesterol measurement. Furthermore, just 55% of this group had been prescribed a statin, and just 53% of those receiving a statin were being treated to target. The outcome was that just

14.2% of the original 78,600 patients had achieved a target total cholesterol level of <5mmol/l.⁶

“The findings show that, in terms of secondary prevention, there is significant room for improvement”, said Dr Boyle. “The vast majority of patients are not being treated to target and, when introduced, the more stringent lipid targets will be even more difficult to achieve,” he added.

Dr Boyle reminded those attending the meeting that there is a substantial body of evidence to support the fact that reducing cholesterol levels significantly improves outcome. Evidence from nine international trials involving more than 60,000 patients clearly demonstrates that not only does lowering cholesterol reduce the associated risk, but it also shows that those patients at highest risk of an event reap the most benefit, he said.

In addition, he pointed out that the Heart Protection Study had revealed that reducing cholesterol was beneficial for at-risk patients, irrespective of baseline cholesterol levels.³ Furthermore, results from the PROVE-IT study suggested that more intensive lipid-lowering treatment produced more significant benefits.⁷

The evidence is there to encourage the medical community to aggressively target lipid levels, said Dr Boyle. The problem, however, is that getting patients to these targets is often difficult and extremely time-consuming, he acknowledged.

“The management of hypercholesterolaemia is resource intensive,” said Dr Boyle. “When we add the patient dimension to that particular mix, including education and incentivising the patient to stay on the same management wavelength, the situation becomes extremely difficult.”

“We know that decreasing cholesterol improves outcomes. We know that those at highest risk will be the ones that do better. But we also know that in a resource depleted environment, as our health service is, and when you bring in other issues such as compliance, this is a real management dilemma,” said Dr Boyle.

He suggested that Inegy would serve as a valuable tool in addressing these management issues. Inegy has the ability to achieve target lipid levels with few titration steps.⁸⁻¹¹ It consequently has implications for physicians, but also provides an opportunity to improve patient compliance by combining two agents in one tablet.

“This is a product which I strongly believe will go a long way towards easing and simplifying the treatment of hypercholesterolaemia for patients and physicians alike,” said Dr Boyle.

Dr Carl Vaughan, consultant cardiologist, Mercy University Hospital, Cork, agreed. He reminded doctors that the body sources cholesterol in two ways; firstly, through biosynthesis in the liver and, secondly, through absorption of dietary cholesterol and bile acids in the intestine. Inegy will allow the treating physician to target both these sources and subsequently improve efficacy, he said.¹²

Statins, which remain the first-line treatment in hyperlipidaemia, block the production of cholesterol by inhibiting HMG-CoA reductase in the liver. However, we also need to address the cholesterol delivered to the intestine, the majority of which is not from dietary sources but rather from free cholesterol biliary secretions from the liver. In total, daily intestinal cholesterol is 50% from biliary cholesterol, 30% from dietary sources and the remaining 20% is produced through the sloughing of intestinal epithelial cells," said Dr Vaughan.¹³

The efficacy of statins in lowering LDL cholesterol has been extensively demonstrated in clinical trials, he said. However, these drugs only target one source of cholesterol. If we are to stand any chance of achieving current targets and emerging, tighter therapeutic goals, both sources of cholesterol must be targeted, said Dr Vaughan.

Dr Vaughan referred to ezetimibe, which targets the absorption of cholesterol in the intestine at the cellular level. It is now believed that ezetimibe blocks the 'pore' through which intestinal cholesterol is absorbed, Dr Vaughan told the meeting. He reported that research published in 2004 had identified the protein involved central to the absorption process. It is now believed, he said, that ezetimibe exerts its effect by blocking this Niemann-Pick C1 like 1 protein or an associated protein.¹⁴

Consequently, he said, combining the effects of a statin with that of ezetimibe served to effectively and aggressively attack both sources of cholesterol. Clinical research supports this approach, according to Dr Vaughan. Compared to statin monotherapy, the new combination therapy shows significantly better results, he said.

In a recently published clinical trial, Inegy 10mg/20mg (which contains 10mg of ezetimibe and 20mg of simvastatin) produced a greater reduction in LDL than with atorvastatin 10mg alone. With atorvastatin 10mg, LDL decreased by an average of 36.1% compared to an average decrease of 50.6% with the new combination product.⁹ Effects on HDL cholesterol, which are now receiving more attention, were also greater.

Dr Vaughan added that studies in more than 3,200 patients have established that the tolerability and safety of the combination product is similar to simvastatin monotherapy in terms of all adverse events, serious adverse events, treatment-related adverse events and discontinuations as a result of side effects.¹⁵

He recommended the use of Inegy in the management of hypercholesterolaemia, where patients have not been adequately controlled on a statin alone. Treatment should be combined with adequate dietary and lifestyle advice.

Inegy is available in three dose formations, each of which

contains 10mg of ezetimibe and 20mg, 40mg and 80mg of simvastatin, respectively.

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