Niacin Laropiprant combination in the management of dyslipidemia: a novel pharmaceutical formulation.

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Abstract

This review describes a novel combination of niacin with laropiprant, which helps improve the tolerability of niacin, which helps improve the tolerability of niacin, while retaining its efficacy. This combination will allow niacin to fulfill its hither to unused potential as a potent HDL –increasing and LDL –lowering drug.

INTRODUCTION

A joint statement released recently by American Diabetes association (ADA) and the American College of Cardiology(ACC) emphasizes the clinical importance of lipoprotein risk factors other than low density lipoprotein cholesterol (LDL-C) in patients at high risk for cardiovascular disease (1). The ADA –ACC consensus statement recommends non –high density lipoprotein HDL-C goals of less than 100 and less than 130 mg/dl, respectively and Apo B goals of less than 90 and less than 80 mg/dl, respectively, for high risk patients without established heart disease and for highest risk patients who have heart disease or who have diabetes and other cardiovascular risk factors (1).

However, we are unable to achieve these levels in two –thirds of our patients, in spite of optimal use of statins (2).

This has led to an increased focus on other hypolipidemic agents, such as niacin .Niacin is a potent and effective lipid lowering drug which has been underutilized because of lack of awareness of its benefit and its side effect of flushing. It may also have been used less often because crystalline niacin is not a patented drug, and hence, is not aggressively marketed by any pharmaceutical major.

Recent advances in the pathophysiology and biochemistry of hyperlipidemia , the current focus on non –LDL targets, the aggressive approach in controlling lipids, tighter and lower targets, the epidemic of metabolic syndrome , including dyslipidemia, and advances in pharmacology, have all combined to increase interest in niacin.

This article reviews the past, present and future of niacin, and highlights the therapeutic advances which should help niacin be utilized optimally for the management of hyperlipidemia in future.

EFFICIACY OF NIACIN

Niacin (nicotinic acid) is a water soluble B vitamin used to treat dyslipidemia for over 50 years(3-5). The Coronary Drug Project, a large scale placebo controlled trial conducted between 1966 and 1975, demonstrated that niacin reduces coronary heart disease events: a 27% reduction in nonfatal myocardial infarction (MI) and 15% reduction in the combined endpoint of nonfatal MI and death were observed compared with placebo-treated patients(6). A 15 year follow-up of the Coronary Drug Project revealed that patients in the niacin group had an 11 % reduction in total mortality compared with those in the placebo group(7).

Two angiographic trials provided evidence that niacin co administered with the bile acid sequestrant colestipol caused either regression or slowed progression of coronary stenosis or atherosclerosis(8,9). In the HDL-Atherosclerosis Treatment Study (HATS), simvastatin plus slow-release niacin resulted in significant regression of coronary stenosis (10) versus placebo, as well as a reduction in cardiovascular events.

PAST IMPROVEMENTS

Niacin is underutilized in clinical practice because of the associated cutaneous flushing of the face and trunk.(11)

Different pharmaceutical formulations have been made to reduce this side effect. Slow release niacin has a dissolution

time of over 12 hours and reduced flushing but is associated with increased hepatotoxicity .Extended release(ER) niacin formulation has an absorption time of 8 to 12 hours, reduced flushing, and an acceptable hepatic safety profile However, it requires a four step, gradual titration regimen over 3 months to reach the efficacious 2 g dose. Clinically meaningful lipid efficacy requires ER niacin doses of at least 1 g/day, hence it take over 1½ months for patients to reach this dose.

Other authors have used pre -treatment with aspirin (12) or indomethacin (13) to mitigate the flushing caused by niacin. These methods have been used as flushing is thought to be mediated by prostaglandins. (14).

NOVEL IMPROVEMENTS

Laropiprant is a novel prostaglandin D1 inhibitor which suppresses the flushing due to niacin. An extended release niacin and laropiprant combination is now available which offers the efficacy of niacin along with an enhanced safety profile (11).

Laropiprant has been shown to significantly suppress vasodilatation induced by ER niacin and improve patient-reported flushing symptoms, more than pre - treatment with aspirin .This correlated with a reduction in the skin vasodilatation as quantified with laser Doppler perfusion imaging (15).

An 8 week, placebo controlled, parallel group study designed to determine the dose -response relationship of laropiprant mediated inhibition of flushing during the initiation phase of treatment (week 1) and during the maintenance phase (week 2 onwards) showed significant reduction in niacin induced flushing compared with ER niacin alone .The beneficial effects of niacin on lipids were not affected(16).

Laropiprant administered at 37.5 mg (rounded to 40 mg and given as two 1g/20 mg tablets) was found to be the minimum dose that maximally protects against flushing associated with chronic use of niacin .Laropiprant in a dose of 20mg provides maximum protection against the flushing associated with the one tablet starting dose of 1 g niacin (11).

A two step dose advancement regimen (1g/20 mg for 4 weeks followed by 2 g/40 mg for chronic maintenance) was selected for subsequent studies to ensure that patients receive a minimally therapeutic 1 g dose of niacin at the initiation of therapy.

EFFICACY RESULTS

In a randomized, placebo controlled (Study 020), dyslipidemic patients (67% on statins) were randomized to ER niacin /laropiprant (n=800), ER niacin (n=543), or placebo (n=270).ER niacin/laropiprant 2g/40 mg produced significant and durable reduction of plasma LDL C levels (-18.4%) The LDL-C lowering efficacy of ER niacin /laropiprant was similar whether it was administered as monotherapy (i.e without statin background treatment, -17.4%) or as combination therapy with statins (-18.9%).(17).

In another study (Study 022), 1398 subjects were randomized equally to ER niacin/laropiprant 1g/20 mg and simvastatin (10, 20, or 40 mg) once daily for 4 weeks. At week 5, treatment doses were doubled in all groups except simvastatin 40 mg (unchanged) and ER niacin/laropiprant 1g /20mg plus simvastatin 40 mg (switched to ER niacin/laropiprant 2 g/ 40 mg plus simvastatin 40 mg).Larger reductions in LDL-C levels were evident with the co-administration of ER niacin/laropiprant 2g /40 mg plus simvastatin compared with ER niacin/laropiprant or simvastatin alone (18).

In both studies a tendency was noted for the LDL C lowering to plateau after 8 to 12 weeks of treatment (4 to 8 weeks at 2g) and remain stable thereafter (17,18)

Niacin also effectively raises HDL-C In study 022 , ER niacin/laropiprant produced significant increases of 23% to 28 % in HDL-C, whether administered alone or with simvastatin irrespective of baseline LDL-C, HDL-C, or TG levels. Similarly increases in HDL-C also were observed in Study 020.Reductions in triglyceride levels were consistent across patient subgroups defined by age, gender, race, baseline lipid values and diabetes mellitus status.

It is noteworthy that no other available drug has the potency to increase HDL –C to such an extent. Niacin therefore holds the promise of emerging as the drug of choice for patients with low HDL, provided its side effects are minimized (19). This is where the safety profile of niacin /laropiprant comes into picture.

SAFETY RESULTS

During the initiation of therapy(week 1),patients treated with ER niacin/laropiprant experienced significantly less flushing than did patients receiving ER niacin, Fewer patients

experienced moderate, severe or extreme flushing (31 % vs.56 % P<0.001) or severe and extreme flushing (14 % vs,33 %, P<0.001).

At the end of the treatment period, patients in the ER niacin/laropiprant group had 0.2 days per weeks with moderate, severe, or extreme flushing versus 0.7 days per week in the ER niacin group .60 % of patients receiving ER niacin 2g reported at least one episode of moderate or greater flushing throughout the period between weeks 6 and 24.

A phase III head to head study (study 054) was also conducted to assess the novel 1g 2g ER niacin/laropiprant abbreviated dosing regime compared with niacin ER, administered for 16 weeks, in the evening with food (11).Patients were allowed to take aspirin as needed to prevent flushing.

Patients treated with rapidly advanced ER niacin/laropiprant experienced significantly (p<.001) less flushing than those treated with gradually titrated ER niacin The flushing signal gradually declined after week 5 in the ER niacin/laropiprant group. It remained elevated in the group treated with ER niacin, with increases at each titration week. Laropiprant can reduce the intrinsic flushing signal of a 1g ER niacin dose to less than that of a 0.5 g dose of niacin ER monotherapy. The tolerability differences grew larger during the ensuring weeks of the study. Superiority of the 1g increased to 2g

ER niacin /laropiprant dosing regimen was observed in the setting of patients having the option of taking aspirin or NSAIDS to help alleviate flushing symptoms.

In study 020, 10% in the ER niacin/laropiprant and 22 % in the ER niacin groups discontinued therapy because of flushing over the 6 month study (p<.001) In study 054, the figures respectively were 7% and 12 % over 16 weeks. ER niacin/laropiprant and ER niacin/laropiprant groups.

ER niacin/laropiprant and ER niacin produced small increases in fasting blood glucose levels (approximately 4 mg /dl median change from baseline), consistent with the known effects of niacin. Very few patients in the pooled population met a prescribed criterion for new onset diabetes in both studies.

There was no difference between the treatment arms with respect to cardiovascular events. Cardiovascular outcomes are being assessed in the ongoing 4 year, 20,000 patient clinical outcome study, the Heart Protection Study Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE).

SUMMARY

ER niacin/laropiprant produces superior lipid- altering efficacy relative to placebo, whether administered as monotherapy or co administered with concomitant statin. Co administration of ER niacin/laropiprant with simvastatin is highly efficacious at producing beneficial changes across the lipid profile. The lipid effects of ER niacin/laropiprant 2g/40 mg are maintained over 52 weeks.

Laropiprant mitigates niacin induced flushing. .ER niacin/laropiprant, combination, therefore offers the opportunity for a major therapeutic advance in the management of dyslipidemia. It allows patients and physicians to utilize the full benefits of niacin, including lowering of LDL, triglycerides, and improving HDL, without significant safety or tolerability issues.

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