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Treatment resistant dyslipidaemia

managing patients who respond poorly to lipid monotherapy

When lipid monotherapy fails to control resistant dyslipidaemia, combination therapy should be the next step. Tailoring the right drug combination to the right type of dyslipidaemia needs to be based on sound knowledge of the synergistic actions and safety of the combination being considered.

DAVID SULLIVAN
MB BS, FRACP, FRCPA

Professor Sullivan is Clinical Associate Professor of Biochemistry at the School of Molecular and Microbial Biosciences, University of Sydney, and Director of the Lipid Clinic at Royal Prince Alfred Hospital, Camperdown, Sydney, NSW.

Optimal control of plasma lipid levels protects against the clinical sequelae of hyperlipidaemia, which include atherosclerotic cardiovascular disease (CVD) and pancreatitis (Figure 1).[1] Difficulty in achieving adequate control of lipid levels may arise for several reasons (Table 1). In patients in whom lipid disturbances are secondary to another condition, such as diabetes or hypothyroidism, it is a prerequisite that the underlying disorder be eliminated or treated as fully as possible (Table 2). This needs to be done to optimise the response of the patient's lipid profile to the specific lipid modifying therapy.

This article discusses the management of specific clinical situations where lipid monotherapy is inadequate in terms of the following underlying lipid abnormalities:

- predominant hypertriglyceridaemia

IN SUMMARY

- **Monotherapy for the treatment of dyslipidaemia can fail for many reasons, including poor patient compliance, the use of an inappropriate agent, side effects, drug interactions and failure to control causative and/or exacerbating factors.**
- **If a patient's untreated low-density lipoprotein cholesterol (LDL-C) level exceeds 6 mmol/L, the very low LDL-C targets required for patients at high-risk of cardiovascular disease may be difficult to reach using monotherapy.**
- **Combination treatments need to be selected on the basis of their synergistic mechanisms and safety profiles.**
- **Fibrates and fish oil n-3 long-chain fatty acids are considered first-line treatments for hypertriglyceridaemia.**
- **Predominant hypercholesterolaemia is best treated initially with a statin and if there is a poor response, the addition of either a cholesterol absorption inhibitor or a bile acid sequestering resin may be needed.**
- **Combination treatment using a statin and either fish oil or fenofibrate is usually required to treat mixed hyperlipidaemia.**

Table 1. Causes of treatment resistance

- Failure to control causative or exacerbating factors
- Lack of effective monotherapy (e.g. mixed hyperlipidaemia or low high-density lipoprotein levels)
- Poor patient compliance
- Selection of inappropriate agent
- Severity of underlying dyslipidaemia
- Treatment-specific side effects or drug interactions

Table 2. Causes of secondary hyperlipidaemia

Predominant hypertriglyceridaemia

- Alcohol excess
- Drug therapy – e.g. beta-blockers, oestrogen, bile acid sequestrants, corticosteroids
- Insulin resistance
- Metabolic syndrome
- Obesity
- Renal impairment
- Type 2 diabetes

Predominant hypercholesterolaemia

- Anorexia nervosa
- Biliary obstruction and primary biliary cirrhosis
- Hypothyroidism
- Nephrotic syndrome

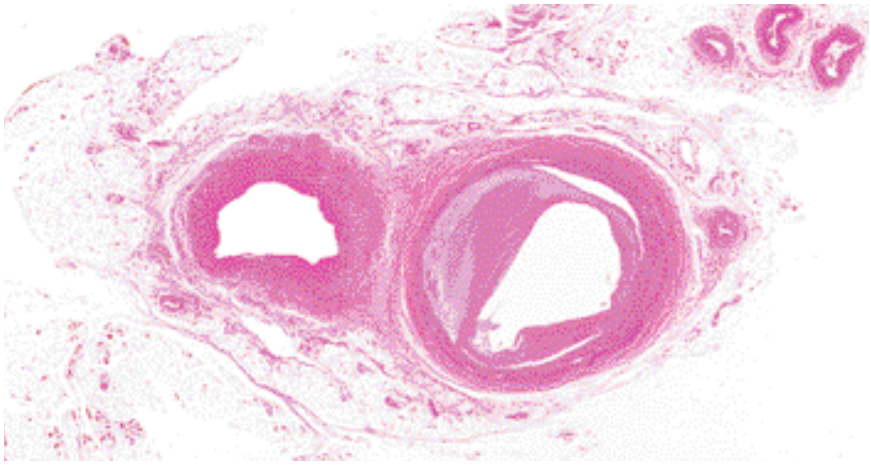

Figure 1. Light micrograph of a section through vessels showing the atherosclerotic process.

- predominant hypercholesterolaemia
- mixed hyperlipidaemia.

The prevalence of these conditions varies according to the arbitrary cut-off levels for the relevant lipid levels. It is more important, however, to recognise that social changes have produced an epidemic of obesity and insulin resistance, which has led to an increase in the prevalence of dyslipidaemia involving triglyceride elevation. Predominant hypercholesterolaemia is usually self-evident. Predominant hypertriglyceridaemia can be regarded as a fasting triglyceride (TG) level above 4 mmol/L without elevation of low-density lipoprotein cholesterol (LDL-C). Mixed hyperlipidaemia includes elevated TG and LDL-C levels. It may be difficult to differentiate predominant hypertriglyceridaemia from mixed hyperlipidaemia because total cholesterol may be elevated in both instances and the LDL-C level cannot be calculated when the TG level is higher than 4 mmol/L. Despite the difficulty in differentiating these two conditions, in this context, the management approaches are similar.

Controlling dyslipidaemia with combination therapy

One of the main themes of this article is the value of combinations of lipid modifying agents, which may be selected on the basis of synergistic mechanisms of action and demonstrated safety (Tables 3 and 4).[2,3] In some instances, the difficulty in achieving adequate lipid control with monotherapy may stem from the severity of an underlying disturbance in lipid metabolism. For example, it may be difficult to control the TG level with a single agent if the untreated level exceeds approximately 10 mmol/L, a level beyond which there is a risk of acute pancreatitis.

Monotherapy may also be insufficient to achieve the very low level of LDL-C recommended for patients at high-risk of CVD if the untreated LDL-C level exceeds approximately 6 mmol/L. Some individual agents effectively reduce cholesterol more than triglycerides and others more effectively lower triglycerides than cholesterol. Nicotinic acid helps to reduce both cholesterol and triglycerides fairly equally but tolerability is a problem for many patients. For this reason, it is likely that the treatment of mixed hyperlipidaemia will require c o mbination therapy.

Patients with low levels of high-density lipoprotein cholesterol (HDL-C) may also require combination therapy because there is a strong inverse relation between TG and HDL-C. This means that patients with low HDL-C levels usually have high TG levels and respond best to exercise, weight loss and triglyceride-lowering therapy.[4] In addition, the minority of patients who have low HDL-C in isolation are usually best treated with nicotinic acid or fibrates, but the response to currently available therapy is often suboptimal.

Table 3. Treatment approaches for resistant hyperlipidaemia

	Predominant hypercholesterolaemia	Predominant hypertriglyceridaemia	Mixed hyperlipidaemia
First-line treatment	Statins	Fibrates or Fish oil	Statin and fish oil or Ezetimibe and a fibrate or Nicotinic acid
Second-line treatment	Combine statin with ezetimibe if patient resistant to first-line treatment	Combine fibrate and fish oil if patient resistant to first-line treatment	Consider a statin (start at low dose) plus fenofibrate with careful monitoring
Third-line treatment	Add nicotinic acid or a bile acid sequestering resin	Add nicotinic acid if patient resistant to second-line treatment	Increase statin dose Consider nicotinic acid
Comments	Titrate statins Monitor lipid levels, also monitor CK and LFTs if patient is symptomatic	Titrate fish oil Monitor lipid levels, also monitor CK and LFTs if patient is symptomatic.	Monitor for side effects Combination treatment needed if TG or LDL-C >4 mmol/L

Abbreviations: CK = creatinine kinase; LFTs = liver function tests; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

Managing predominant hypertriglyceridaemia

First-line treatment

Predominant hypertriglyceridaemia is discussed first because it is the clinical situation where the inappropriate use of HMG-CoA reductase inhibitors (statins) occurs most frequently.

Lifestyle modifications

Patients with predominant hypertriglyceridaemia require aggressive lifestyle intervention to address:

- obesity
- inactivity
- alcohol excess
- uncontrolled diabetes.

Massive hypertriglyceridaemia (a TG level greater than 10 mmol/L) may require more aggressive management and limitation of dietary fat intake to below 10 to 20% of energy derived from fat.

Fibrates

Fibrates are the first-line drug therapy for hypertriglyceridaemia. These drugs act by stimulating the peroxisome proliferator-activated receptor (PPAR)-alpha, which controls the expression of gene products that mediate TG metabolism. As a result, synthesis of fatty acids, TG and very low-density lipoproteins (VLDL) is reduced. TG catabolism by lipoprotein lipase is enhanced and apolipoprotein A-1 production is up-regulated, which enhances TG catabolism and HDL synthesis.

Fibrates usually reduce TG levels by up to 50% and increase HDL-C levels by up to 20%, but changes in LDL-C levels are variable and patients with diabetes may have blunted responses. Despite this, studies of patients receiving fibrate therapy have reported reduced rates of CVD, especially among those with low HDL-C levels or insulin resistance and/or diabetes.[5]

The profile and frequency of side effects associated with the use of fibrates are similar to those of statins. Like statins, these drugs are generally well tolerated by patients but they can increase the risk of cholelithiasis and prolong the action of concomitantly administered anticoagulants.

Fish oil and nicotinic acid

Fish oil provides an alternative first-line treatment for hypertriglyceridaemia. It contains highly polyunsaturated long-chain n-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both EPA and DHA inhibit endogenous TG synthesis due to their long fatty acid chains and maximal extent of polyunsaturation.

EPA and DHA comprise approximately 33% of the fatty acids in fish oil and an intake of greater than 2 g of n-3 fatty acid daily (6 g of most forms of fish oil) can lower TG levels in a dose dependent fashion by up to about 50%.

Changes in LDL-C level and HDL-C level associated with EPA and DHA are variable. Fish oil fatty acids are also known to inhibit platelet aggregation, and some studies indicate they may improve cardiac rhythm disturbances. In addition, trials suggest that fish oils may reduce mortality from coronary heart disease (CHD).[6] These agents appear to be safe and well tolerated.

Second-line treatment

Combination treatment

If target TG levels cannot be reached using fibrates, fish oil or nicotinic acid, then combination treatments should be considered. The initial treatment target for patients with predominant hypertriglyceridaemia is a TG level below 10 mmol/L to reduce the risk of acute pancreatitis.

continued

Table 4. Drugs for treating resistant dyslipidaemia

Drug	Action	Comments
Bile acid sequestering resins	Prevent reabsorption of bile acids, which leads to increased *de novo* bile acid synthesis from hepatic cholesterol. Depletion of hepatic cholesterol up-regulates LDL-receptor activity and reduces LDL-C levels synergistically with statins.	• Can achieve substantial reductions in LDL-C and modest increases in HDL-C • TG levels may rise • May affect bioavailability of other drugs • Can be poorly tolerated
Ezetimibe	Inhibits cholesterol absorption via an intestinal mucosal cholesterol transporter protein, which then depletes hepatic cholesterol and up-regulates hepatic LDL-receptor activity.	• Can reduce LDL-C by 15-20%, which increases to 17-25% when combined with statins • Limited effect on TG and HDL-C
Fibrates	Control the expression of gene products that mediate TG metabolism, which reduces the synthesis of fatty acids, TG and VLDL.	• Can reduce TG by 50% • Can reduce HDL-C by 20%
Fish oil	Contains polyunsaturated long-chain fatty acids EPA and DHA, which inhibit endogenous TG synthesis.	• Can reduce TG by 50%
Nicotinic acid	Decreases the release of peripheral fatty acid and therefore reduces synthesis of LDL and its precursor.	• Side effects include flushing, gastric irritation and abnormal LFTs
Plant sterols	Inhibit intestinal cholesterol reabsorption by disrupting intestinal micelle formation. This reduces the bioavailability of cholesterol and some lipid micronutrients but not triglycerides.	• Can reduce LDL-C by 7-15% • Also reduce fat-soluble nutrients – e.g. carotene
Statins	Inhibit cholesterol synthesis and up-regulate the activity of LDL receptors leading to increased LDL clearance. Secondary reduction of LDL synthesis by enhanced removal of the precursor to LDL. May have pleiotropic effects – e.g. suppression of inflammation.	• Can reduce LDL-C by 60% • Can reduce TG by 40% • Can raise HDL-C by 10% • Need to monitor creatinine kinase levels if muscle symptoms arise

Abbreviations: LDL = low density lipoprotein; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; VLDL = very low density lipoprotein; LFTs = liver function tests; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Responses can be dramatic and gratifying when patients implement major changes in lifestyle. Conversely, responses are often disappointing if diet, exercise and/or alcohol problems persist. A patient's medium- to long-term risk of CVD may be increased unless TG and HDL-C levels return to near ideal levels, which are defined as a TG level below 2 mmol/L and an HDL-C level greater than 1 mmol/L.

Persistent hypertriglyceridaemia is usually associated with adverse qualitative changes in low-density lipoproteins, which become small and dense. Consequently, the LDL-C level underestimates the risk of CVD in this situation and consideration should be given to the careful addition of a statin to reduce this risk.

Third-line treatment

Nicotinic acid, which is discussed in the section on mixed hyperlipidaemia, also effectively reduces TG levels.

Managing predominant hypercholesterolaemia

First-line treatment

Predominant hypercholesterolaemia is treated with a combination of dietary changes and a statin in a sufficient dose to achieve target LDL-C levels. Statins act by inhibiting the synthesis of cholesterol, which up-regulates the activity of the LDL receptor, thereby increasing LDL clearance. Statins also enhance removal of intermediate density lipoprotein (IDL), the precursor to LDL, resulting in a secondary reduction in LDL synthesis.

Statins are established as the first-line therapy for predominant hypercholesterolaemia. They can reduce LDL-C by up to 60% and TG levels by up to 40% and raise HDL-C levels by up to 10%. So-called 'pleiotropic effects' such as suppression of the inflammatory response may also arise due to suppression of intermediate metabolites like isoprenes. Statins are generally well tolerated and serious side effects are rare.[2]

Safety reviews have been reassuring about concerns over long-term hepatic damage associated with statins, even following isolated elevations of alanine transaminase.[2] However, clear evidence of muscle side effects and/or a creatinine kinase (CK) elevation 10 times above the upper limit of normal may limit the use of

these medications.

When patients do not reach LDL targets on the highest tolerated statin dose, the use of agents that act in the intestine, such as ezetimibe (Ezetrol), plant sterols or resins, is warranted. These agents may also be introduced when patients do not tolerate statins.

Second-line treatment

Several second-line therapeutic options are available for the treatment of predominant hypercholesterolaemia.

Ezetimibe

Ezetimibe inhibits cholesterol absorption via the intestinal mucosal cholesterol transporter Niemann-Pick C1 Like 1 protein. Failure to absorb dietary and biliary cholesterol depletes hepatic cholesterol and up-regulates hepatic LDL receptor activity. The standard 10 mg/day dose of ezetimide reduces LDL-C by 15 to 20% with little, if any, effect on either TG or HDL-C. When ezetimibe is used in combination with statins, a slightly greater LDL-C reduction of approximately 17 to 25% occurs. Ezetimibe appears to be well tolerated by patients but its effect on CVD endpoints is yet to be determined.

Simvastatin plus ezetimibe

Simvastatin and ezetimibe have been combined in a fixed-dose formulation known as Vytorin in order to make this effective form of combination therapy more convenient and affordable.

Plant sterols

Plant sterol supplemented foods (e.g. some margarines, milks and yoghurts) inhibit cholesterol absorption by a different mechanism. They compete with cholesterol in the intestinal emulsion and impair the formation of the micelles that are required for intestinal cholesterol absorption. This reduces LDL-C by 7 to 15%. Plant sterols do not interfere with fat absorption but they do reduce the level of some fat-soluble nutrients, particularly carotene.[7]

Third-line treatment

Bile acid sequestering resins

Bile acid sequestering resins, such as cholestyramine (Questran Lite) and colestipol (Colestid Granules For Oral Suspension), bind bile acids in the intestine thereby preventing their reabsorption. This action is compensated for by an increase in *de novo* bile acid synthesis from hepatic cholesterol via the enzyme 7-alpha hydroxylase. The resultant depletion of hepatic cholesterol up-regulates LDL-receptor activity and reduces LDL-C levels.

Resin monotherapy can achieve a substantial reduction in LDL-C levels and a modest increase in HDL-C levels but TG levels may also rise. Even low doses of resins provide a useful synergistic effect to the action of statins. While resin monotherapy is safe, it is poorly tolerated and may interfere with the bioavailability of other drugs. Future improvements in the tolerability of this class of drugs are expected with the advent of new formulations. Specific inhibitors of the intestinal bile acid transporter system are also likely to become available in the future. These developments may rekindle interest in this class of cholesterol lowering drugs.

Combination treatment

The combination of an inhibitor of cholesterol synthesis (a statin) and an inhibitor of intestinal absorption of cholesterol (ezetimibe) is particularly effective for two reasons. Statin therapy is counteracted by a compensatory increase in intestinal cholesterol absorption, whilst ezetimibe therapy is counteracted by a compensatory increase in cholesterol synthesis. The combination of the two agents provides mechanisms of action that are complimentary. Furthermore, each mechanism of action counteracts the compensatory response to the other medication.

The mechanism of action of bile acid sequestering resins is sufficiently different from the other agents used to treat predominant hypercholesterolaemia that it also offers a further mild synergistic effect.

Nicotinic acid may also be used to reduce LDL-C levels and acts synergistically when combined with a statin. Despite the synergistic action, caution is recommended when combining nicotinic acid with a statin because the risk of side effects may be marginally increased.

It is important to note that oestrogen replacement therapy, which may reduce LDL-C levels and increase HDL-C levels and TG levels, is no longer recommended for CVD prevention in postmenopausal women.

Managing mixed hyperlipidaemia

First-line treatment

Mixed hyperlipidaemia can be difficult to treat. Statin monotherapy is often inadequate when fasting TG exceeds approximately 4 mmol/L and fibrate monotherapy struggles to address the cholesterol component unless it is due to remnant particles.

Nicotinic acid

Nicotinic acid (vitamin B_3 in pharmacological doses) is moderately effective in reducing TG levels, LDL-C levels and lipoprotein(a). At present, nicotinic acid is the most effective agent for increasing HDL-C levels. Its mechanism of action involves a reduction in the release of peripheral fatty acid, which leads to the reduced synthesis of LDL and its initial precursor, VLDL.

Patients taking nicotinic acid universally experience flushing, while other side effects include gastric irritation, liver function disturbances, exacerbation of gout and hyperglycaemia. Using a slow-release formulation, which is yet to be made available in Australia, and/or dosing approximately 15 minutes after the patient takes low-dose aspirin or adding of one of the newly developed prostaglandin receptor agonists may reduce flushing. Clinical trials involving nicotinic acid suggest this agent has

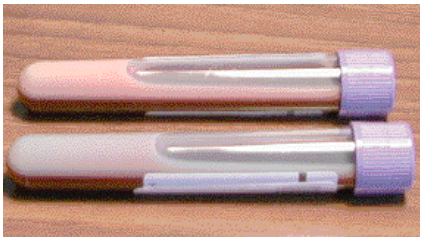

Figure 2. Milky plasma collected from a patient with massive hypertriglyceridaemia.

clinical benefits including reducing atherosclerosis and cardiovascular events.

Second-line treatment

Combination treatment

Mixed hyperlipidaemia frequently requires combination therapy. A statin and fish oil combination is relatively safe and effective when the TG level is not very high. A fibrate and ezetimibe combination has also been shown to be effective.[8]

Other options include the combination of a statin with nicotinic acid or a statin with a fibrate. These combinations can be effective for the treatment of mixed hyperlipidaemia but the risk of myopathy increases. Recent experience with fenofibrate (Lipidil) and moderate statin doses suggests that fenofibrate and a statin is safer than gemfibrozil and a statin.[5]

Conclusion

Predominant hypercholesterolaemia is best treated with statin therapy. Resistant cases may require the addition of a cholesterol absorption inhibitor such as ezetimibe or a bile acid sequestering resin. Predominant hypertriglyceridaemia is best treated with a fibrate or fish oil and resistant cases may warrant a combination of the two agents. Although statin therapy is unlikely to assist severely hypertriglyceridaemic patients, it may be warranted in milder cases with increased CVD risk. Treatment of mixed hyperlipidaemia usually requires a combination of fish oil with a statin or fenofibrate combined with a statin. MT

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DECLARATION OF INTERESTS: Professor Sullivan is a member of advisory boards for the following pharmaceutical companies: Sanofi-Aventis Australia, Merck Sharp and Dohme, Schering Plough, Solvay, Pfizer and AstraZeneca.