

Dyslipidemia:

When the Usual Statins Are Not Enough



David Blank, MDCM, FRCPC (Medical Biochemistry)

Presented at McGill University's 38th Annual Course in Drug Therapy, Montreal, Quebec, May 2007.

Coronary artery disease (CAD) is a major cause of morbidity and mortality in Canadians. Hypercholesterolemia, a major risk factor for CAD, requires aggressive treatment.¹ Five classes of medications are used in the treatment of dyslipidemia (Table 1). The most used class of medications to treat dyslipidemias is HMG CoA reductase inhibitors (also known as statins).^{2,3} However, in some cases, statins alone are not sufficient to correct the dyslipidemia.

Statins are used most frequently to treat dyslipidemias.

Combination therapy for dyslipidemia

Combination therapy is useful to maximize the effects and to potentially minimize any dose-related side-effects. Therapy that combines two or more medications can be used to reach therapeutic goals. However, there are pros and cons to this approach. Combination therapy allows for the use of lower doses of a medication and may provide other non-lipid benefits (e.g., fenofibrate can reduce uric acid).⁴

Celine's case

Celine, 62, has dyslipidemia. She smokes one-quarter pack of cigarettes per day. She is active and walks at least 40 minutes per day. Celine follows a good diet and has 2 to 3 glasses of wine per week.

Medical history

Celine's medical history includes:

- hypertension and
- polymyalgia rheumatica.

She does not have a family history of premature coronary artery disease (CAD).

Currently, Celine takes 150 mg of irbesartan q.d. and her BP is 133/70 mmHg.

November 2006 laboratory results

In November 2006, Celine underwent testing and the following was noted:

- Total cholesterol (TC): 8.46 mmol/L
- Triglyceride (TG): 2.84 mmol/L
- HDL-C: 1.41 mmol/L
- LDL-C: 5.76 mmol/L
- TC/HDL-C ratio: 6.0
- Apo B: 1.57 mg/L
- Fasting blood glucose (FBG): 5.1 mmol/L

Her CV risk using the Framingham risk tables was 11% (moderate risk group). The therapeutic target values were:

- TC/HDL-C ratio: < 5
- Calculated LDL-C: < 3.5 mmol/L
- Apo B: < 1.05 mg/L

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Table 1*

Medications used in the treatment of dyslipidemia and their recommended dosage

Statins

- Atorvastatin: 10 mg-80 mg
- Fluvastatin: 20 mg-80 mg
- Lovastatin: 20 mg-80 mg
- Pravastatin: 10 mg-40 mg
- Rosuvasatin: 5 mg-40 mg
- Simvastatin: 10 mg-80 mg

Bile acid resins

- Cholestyramine: 2 g-24 g
- Colestipol: 5 g-30 g

Cholesterol absorption inhibitors

- Ezetimibe: 10 mg

Fibrates

- Bezafibrate: 400 mg
- Fenofibrate: 67 mg-200 mg (45 mg-48 mg)
- Gemfibrozil: 600 mg-1,200 mg

Niacin

- Nicotinic acid: 1 g-3 g
- Extended release: 1 g-2 g

* Adapted from R. McPherson, J. Frohlich, G. Fodor, et al: Canadian Cardiovascular Society Position Statement—Recommendations for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease. *Can J Cardiol* 2006; 22(11):913-27.

In patients who present with mixed dyslipidemia, other combinations with a statin should be considered.

Dr. Blank is a Medical Biochemist; Attending Staff, McGill University Health Centre Lipid Clinic, McGill University Health Centre; and Director, Division of Medical Biochemistry, Royal Victoria Hospital, Montreal, Quebec.

On the other hand, combination therapy can have negative effects, such as increased adverse reactions (*e.g.*, rhabdomyolysis) and higher medication costs.

Although there are some angiographic data supporting combination therapy, currently, there is a lack of outcome studies supporting its use to prevent CAD.⁵

Statins

The most frequently used combination of medication is a statin with another agent. The specific selection of which class of medication to add is dependant upon the required type of change necessary to the lipid profile.⁶ Usually, there is a need for additional LDL-C lowering. This need typically occurs either when a patient has developed myalgias after the statin dose has been increased or when a patient is reluctant to take the maximum statin dose due to a fear of muscular side-effects. Instead of increasing the dose of a statin to its maximum, another medication is then added. Second, when the use of the maximal dose of a statin still does not lead to adequate LDL-C control, another class of medications is added to this maximal dose. Here, a cholesterol absorption blocker (*e.g.*, ezetimibe) or a bile acid resin would be appropriate. Since ezetimibe is usually better tolerated than a bile acid resin, it is more frequently used.

In patients who present with mixed dyslipidemia, other combinations with a statin should be considered. If patients have adequately controlled LDL-C but have persistent hypertriglyceridemia, the addition of a fibrate could help. Unfortunately, this combination has been associated with an increased risk of rhabdomyolysis, especially when a statin is

combined with gemfibrozil. A statin with a fibrate has also been used to raise HDL-C, but fibrates are not the best class of medications available for raising HDL-C; niacin is. Niacin also lowers triglycerides and LDL-C to some extent. Consequently, a statin combined with niacin is useful in some situations. However, niacin has troublesome cutaneous side-effects which limit its use. An intermediate release formulation of niacin is now available in Canada which is better tolerated.

The most common side-effect seen with statins used in combination therapy, like statin monotherapy, is myalgias.

Common side-effects of statins

The most common side-effect seen with statins used in combination therapy, like statin monotherapy, is myalgias. Factors that increase the risk of statin-induced myopathy include the following patient characteristics:

- diet (*i.e.*, grapefruit juice),
- hypothyroidism,
- hepatic dysfunction,
- renal insufficiency,
- female gender,
- increasing age and
- polypharmacy.

Those statins which increase the risk of myopathy are those which:

- are metabolized by cytochrome pathways

Celine's case cont'd...

Celine cannot tolerate atorvastatin, or simvastatin because of her severe myalgia (creatinine kinase remained normal). However, she is able to tolerate 40 mg of pravastatin q.h.s.

September 2007 laboratory results

In September 2007, Celine's new laboratory results are:

- TC: 6.90 mmol/L
- TG: 2.09 mmol/L
- HDL-C: 1.32 mmol/L
- LDL-C: 4.63 mmol/L
- TC/HDL-C ratio: 5.2
- Apo B: 1.26 mg/L
- FBG: 4.9 mmol/L

At this point, since she is still above the treatment goals, 10 mg of ezetimibe q.d. is added to her list of medications.

December 2007 laboratory results

Three months later, Celine has additional blood work done and her results reveal:

- TC: 5.54 mmol/L
- TG: 2.41 mmol/L
- HDL-C: 1.38 mmol/L
- LDL-C: 3.07 mmol/L
- TC/HDL-C ratio: 4.0
- Apo B: 1.04 mg/L
- FBG: 4.9 mmol/L

These results are now within the acceptable range for a moderate-risk individual and Celine reports no significant myalgias. Therefore, she is told to continue the same treatment.

(particularly cytochrome P450 3A4),

- are present in high concentrations,
- have high bioavailability and
- are lipophilic.

A statin combined with a fibrate is the combination most likely to cause myopathies. Fenofibrate appears to be the safest fibrate for use in combination with a statin. Bile acid resins, ezetimibe and niacin, in combination with a statin, appear to be safe.

Take-home message

- There are 5 classes of medications available to treat dyslipidemic patients
- Combination therapy is useful to maximize the effects and to potentially minimize dose-related side-effects
- Balancing the use of the different statins with the use of other medications, either singly or in combination, allows for the treatment of difficult patients when the typical doses of statins do not work

Additional therapy


Occasionally, combination therapy without a statin or a combination using three or more medications is required.

When a patient cannot tolerate any statin but needs LDL-C reduction, ezetimibe could be tried with a fibrate or niacin. In these situations, the patient would also benefit from the triglyceride-lowering and the HDL-C raising effects of additional medications.

The triple combination of a statin, ezetimibe and a bile acid resin could be used when LDL-C reduction, with two medications, is not enough.

When a patient cannot tolerate any statin but needs LDL-C reduction, ezetimibe could be tried with a fibrate or niacin.

Conclusion

In the treatment of patients with dyslipidemias, the use of more than one class of medications can be beneficial and should be considered. Balancing the use of the different statins with the use of other medications, either singly or in combination, allows for the treatment of difficult patients when typical doses of statins do not work. 

References

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