The comment was based on the pivotal clinical trials which used different regimens from the phase II study. In these trials symptoms of neuropathy developed in 85–95% of patients. Anaemia occurred in more than 80% of patients and neutropenia and thrombocytopenia were very common. The comment that most patients will have vomiting and diarrhoea is also consistent with the manufacturer's product information.

In Dr Clarke's trial 83% of the patients required a dose reduction and toxicity resulted in 25% ceasing treatment. While the frequency of severe adverse effects may be low from an oncology perspective, it is important that patients decide what is acceptable to them. The Executive Editorial Board hopes that the favourable response rate seen in the trial will lead to improved survival for the patients.

Medicinal mishap

Statin-fibrate combination therapy

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Case 1

After coronary bypass five years ago this patient was treated with atorvastatin 40 mg daily and gemfibrozil 600 mg twice daily for combined hyperlipidaemia. He also took extended-release diltiazem for hypertension and aspirin 100 mg daily. He complained of minor, tolerable muscle aches but his creatine kinase levels were normal.

In March, cerivastatin 0.3 mg daily was substituted for atorvastatin. Three weeks later, the patient noticed flu-like symptoms with aching of the neck, shoulders and limbs. He persisted with his therapy in spite of severe muscle aching and stiffness, weakness, lethargy and decreasing urinary output. When he presented in April he had signs of acute renal failure and his urine contained pigmented casts typical of myoglobinuria. His creatine kinase peaked at over 30 000 U/L with a high creatinine (0.75 mmol/L) and urea (49.7 mmol/L). His liver function was also affected (LDH 2727 U/L, ALT 1089 U/L, AST 1827 U/L). After haemodialysis for 15 days, his initially profound muscle weakness improved and his strength returned to normal over subsequent weeks, as did his renal function.

Case 2

A 63-year-old woman with combined hyperlipidaemia (total cholesterol 7.5 mmol/L, triglycerides 10.2 mmol/L) was prescribed cerivastatin 0.4 mg daily. Three years previously she had been treated with atorvastatin, but ceased this after six months because of severe muscle aches and pains. Gemfibrozil 600 mg daily was subsequently added to cerivastatin when her total cholesterol and triglycerides were 5.4 and 5.7 mmol/L respectively. Three weeks later, she developed stiffness and pain in the lower back, with severe impairment of mobility. She ceased medications and her symptoms had largely resolved on presentation two days later. Her plasma concentrations were: creatine kinase 14 500 U/L, LDH 647 U/L, AST 352 U/L, ALT 191 U/L. Glucose, creatinine and urea concentrations were normal. TSH was marginally elevated (4.7 mIU/L) and free T4 borderline (11 pmol/L). Two days later her creatine kinase was 45 600 U/L. Her symptoms and creatine kinase concentrations were normal one week later.

Comment

Rhabdomyolysis has been a frequent adverse drug reaction with cerivastatin-gemfibrozil combination therapy. Fatalities have led to the withdrawal of cerivastatin from the market, other than in Japan where gemfibrozil is not available.

High plasma concentrations of 'statins' predispose to rhabdomyolysis with either high doses or co-administration of cytochrome P450 inhibitors, including calcium channel blockers[1] (see Case 1).

Conditions predisposing to myopathy include severe hypoxia, hyperthermia, hypotension, hypothyroidism (see Case 2), recent major surgery, severe acute infections, severe endocrine, metabolic and electrolyte disturbances, uncontrolled seizures and possibly underlying genetic myopathies.[2] Patients experiencing myopathy with one statin are likely to experience it with another (see Cases 1 and 2).

Severe myopathy may occur without elevation of creatine kinase, and therapy should be withdrawn in patients, especially elderly women, complaining of muscle weakness.[3] Patients should have normal thyroid function before starting treatment with lipid-lowering therapy. Adverse drug reactions should be reported to the Adverse Drug Reactions Advisory Committee to ensure adequate post-marketing surveillance.

REFERENCES

1. Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? Aust Prescr 2001;24:10-2.
2. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. Drug Safety 2000;22:441-57.
3. England JD, Walsh JC, Stewart P, Boyd I, Rohan A, Halmagyi GM. Mitochondrial myopathy developing on treatment with the HMG CoA reductase inhibitors – simvastatin and pravastatin. Aust N Z J Med 1995;25:374-5.

Muscle disorders with statins – to August 2001

Statin	*Total number of reports*	*Reports of myalgia, myopathy and myositis (% of total)*	*Reports of rhabdomyolysis (% of total)*
Cerivastatin	148	68 (45.9%)	27 (18.2%)
as monotherapy			7 (4.7%)
with gemfibrozil			20 (13.5%)
Simvastatin	2248	427 (19.0%)	32 (1.4%)
Atorvastatin	679	130 (19.1%)	3 (0.4%)
Pravastatin	339	85 (25.1%)	3 (0.9%)
Fluvastatin	242	62 (25.6%)	1 (0.4%)

Table provided by Adverse Drug Reactions Advisory Committee