REVIEW ARTICLE

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Extending Therapy Options in Treating Lipid Disorders

A Clinical Review of Cerivastatin, a Novel HMG-CoA Reductase Inhibitor

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Abstract

Cerivastatin is a third generation pure enantiomeric HMG-CoA reductase inhibitor. It reduces low density lipoprotein (LDL)-cholesterol by 22 to 44% at doses of 0.1 to 0.8 mg/day. The drug has been extensively evaluated for more than 5 years in clinical trials and is currently marketed in a number of countries at doses of 0.1 to 0.3 mg/day.

Cerivastatin has been tested in more than 4000 patients during extensive phase II and III studies. About 40% of patients in these trials were women, and many participants were aged between 65 and 75 years. The trial populations had moderate to severe hypercholesterolaemia, with mean baseline LDL-cholesterol levels of approximately 5.2 mmol/L (200 mg/dl).

In large phase III trials, cerivastatin, over the dosage range of 0.1 to 0.4 mg/day, reduced LDL-cholesterol by 22.4 to 36.1% from baseline. As with other HMG-CoA reductase inhibitors, the log-linear dose-response curve of cerivastatin showed a 6% additional decrease in mean LDL-cholesterol levels for each doubling of the daily dose, with no plateau effect noted at the highest dosage yet tested (0.8 mg/day). High density lipoprotein cholesterol levels increased by 4 to 10% during cerivastatin therapy. This effect, which was consistent with that of other HMG-CoA reductase inhibitors, was not dose related.

As has been found with other statins, the triglyceride-lowering effects of cerivastatin are dependent on baseline triglyceride levels, with very small reductions occurring in patients with low initial levels [<1.7 mmol/L (150 mg/dl)], and larger dose-dependent reductions of up to 36% with the 0.4 mg/day dose observed in patients with baseline triglyceride levels >2.8 mmol/L (250 mg/dl).

Cerivastatin was well tolerated in all studies. Cerivastatin recipients and recipients of other HMG-CoA reductase inhibitors experienced a similar incidence of adverse events (including hepatic transaminase elevations) in comparative studies.

Cerivastatin is an effective and safe lipid-lowering agent for most patients with hypercholesterolaemia.

Agents that reduce low density lipoprotein (LDL)-cholesterol levels are effective in the primary and secondary prevention of coronary artery disease and, as a class, HMG-CoA reductase inhibitors are the drugs of choice for the treatment of hypercholesterolaemia.[1-3]

A number of generations of HMG-CoA reductase inhibitors are now available commercially: they include first generation agents such as lovastatin, pravastatin and simvastatin, which are produced via a fermentation-based process, and a second generation, fully synthetic racemic compound, fluvastatin. Two third generation agents, atorvastatin and the pyridine derivative cerivastatin, are fully synthetic, pure enantiomeric compounds. This review focuses on the clinical efficacy and tolerability of cerivastatin.

During the last 5 years, cerivastatin has been evaluated in more than 4000 patients (about 40% of whom were women).[4-12] The drug is currently marketed in a number of countries at dosages of 0.1 to 0.3 mg/day. Higher dosages (up to 0.8 mg/day) have been studied, or are currently being studied, in clinical trials, and the 0.4 mg/day dose is expected to be approved for general use in the very near future.

1. Efficacy

To assess efficacy, we used pooled data from the initial pivotal clinical studies; these included 1785 patients (approximately 40% women) with hypercholesterolaemia who received 8 weeks' treatment with cerivastatin 0.1 to 0.4 mg/day or placebo.[12] The mean age of this population was approximately 55 years, and many participants were aged between 65 and 75 years. The patients had moderate to severe hypercholesterolaemia: baseline mean total and LDL-cholesterol levels were approximately 7.5 and 5.2 mmol/L, respectively (290 and 200 mg/dl); the baseline high density lipoprotein (HDL)-cholesterol level averaged 1.3 mmol/L (50 mg/dl). Mean serum triglycerides levels were generally about 2 mmol/L (170 mg/dl).

1.1 Effect of Cerivastatin on LDL-Cholesterol Levels

Cerivastatin dose dependently produced mean reductions in LDL-cholesterol levels of 22.4 to

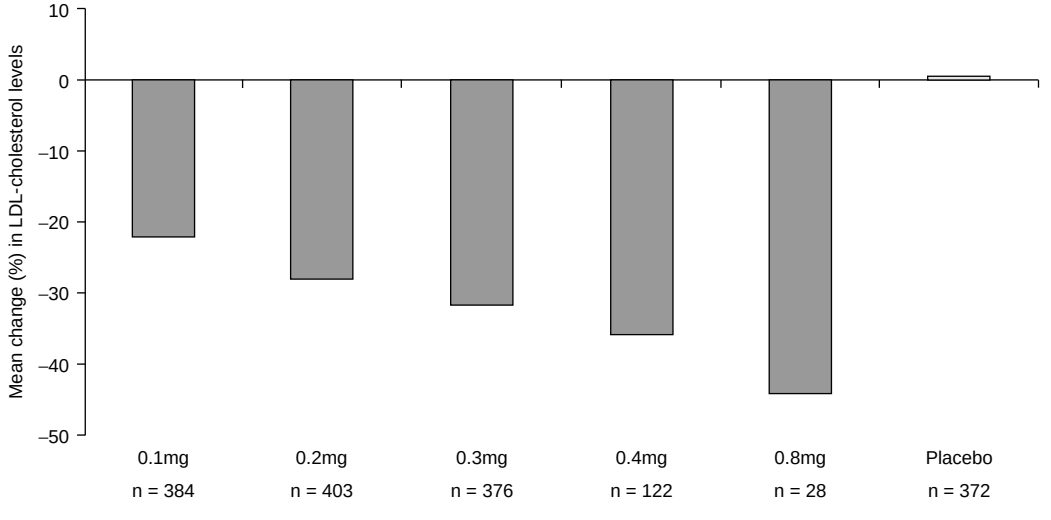

Fig. 1. Mean reductions in low density lipoprotein (LDL)-cholesterol levels from baseline after 8 weeks' therapy with cerivastatin 0.1 to 0.8 mg/day (patients on cerivastatin 0.8 mg/day received only 4 weeks' treatment). Data combined from placebo-controlled studies.[12,13]

44% compared with a 0.3% increase with placebo (fig. 1).[12,13] However, the median LDL-cholesterol reductions were more substantial, with 52% of patients achieving a >35% decrease with cerivastatin 0.3 mg/day (fig. 2). The observed variability in individual responses provides the rationale for starting at lower dosages and titrating upwards on the basis of LDL-cholesterol reductions. A recently completed 4-week phase II study with cerivastatin 0.8 mg/day (n = 28) showed a mean LDL-cholesterol reduction of 44% (fig. 1).[13]

The dose-dependent pattern of increasing LDL-cholesterol reductions observed with cerivastatin is consistent with the known log-linear dose-response curve observed with other HMG-CoA reductase inhibitors:[14] each doubling of the cerivastatin dose yields an approximately 6% additional reduction from baseline LDL-cholesterol levels.

The response to cerivastatin was good in all subgroups of patients with hypercholesterolaemia, with an enhanced reduction apparent in certain groups.[12] In particular, responses in women tended to be better than those in men, irrespective of the cerivastatin dosage (3 to 4% difference in LDL-cholesterol reduction at any dosage level). Similarly, LDL-cholesterol reductions in patients aged ≥65 years were generally 3 to 7% greater than those observed in patients aged ≤40 years.

1.2 Triglyceride-Lowering Effects of Cerivastatin

The triglyceride-lowering effect of cerivastatin, as with all HMG-CoA reductase inhibitors, is highly dependent on baseline triglyceride levels. In patients with low initial triglyceride levels [<1.7 mmol/L (150 mg/dl)], cerivastatin produced only relatively small reductions (6 to 10%), which did not appear to be dose related (fig. 3). In contrast, in patients with a baseline triglyceride level of >2.8 mmol/L (250 mg/dl), cerivastatin was associated with more substantial and dose-related triglyceride reductions, ranging from 16.3% at a dosage of 0.1 mg/day to 36% at a dosage of 0.4 mg/day (fig. 3).

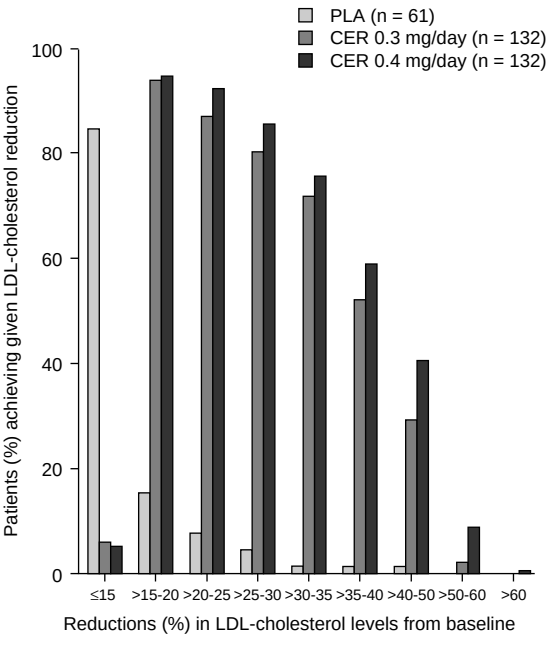

Fig. 2. Percentages of patients receiving cerivastatin (CER) 0.3 or 0.4 mg/day, or placebo (PLA) who achieved specific reductions in low density lipoprotein (LDL)-cholesterol levels from baseline.[12]

1.3 Effect of Cerivastatin on HDL-Cholesterol Levels

Cerivastatin 0.1 to 0.8 mg/day produced moderate increases in HDL-cholesterol levels.[12,13] This effect did not appear to be dose related; however, as shown in figure 4, the observed increase in HDL-cholesterol levels during cerivastatin therapy relates directly to baseline triglyceride levels. In patients with triglyceride levels >2.8 mmol/L (250 mg/dl) and HDL-cholesterol levels of 1.05 mmol/L (40 mg/dl), HDL increases of 10 to 14% were seen (fig. 4).

2. Comparison with Other HMG-CoA Reductase Inhibitors

Cerivastatin has been compared with fluvastatin in a 12-week randomised double-blind, forced

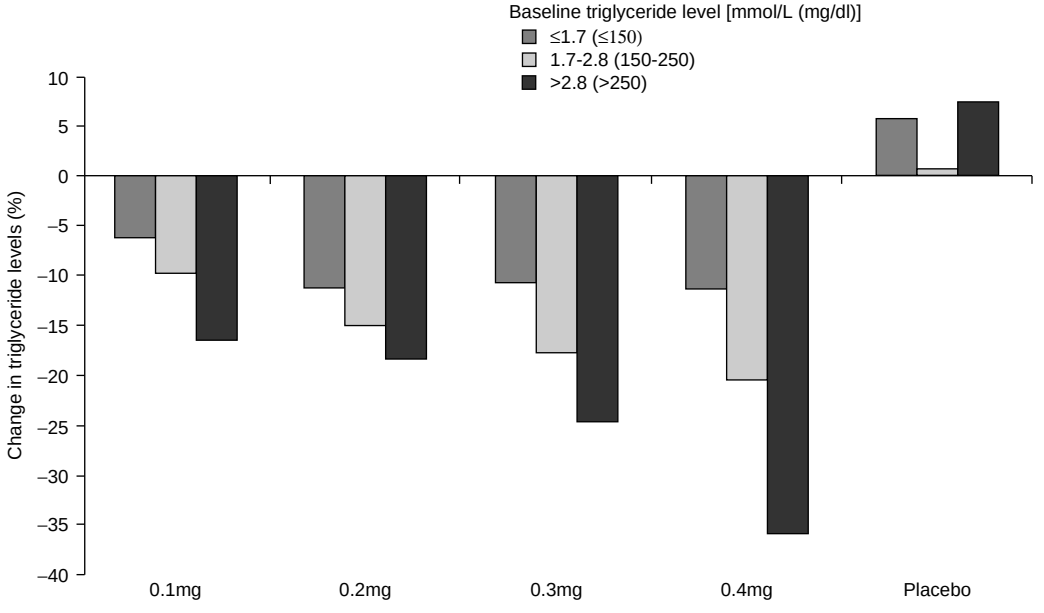

Fig. 3. Changes in triglyceride levels during 8 weeks' therapy with cerivastatin 0.1 to 0.4 mg/day or placebo. Responses are stratified according to baseline triglyceride levels.[12]

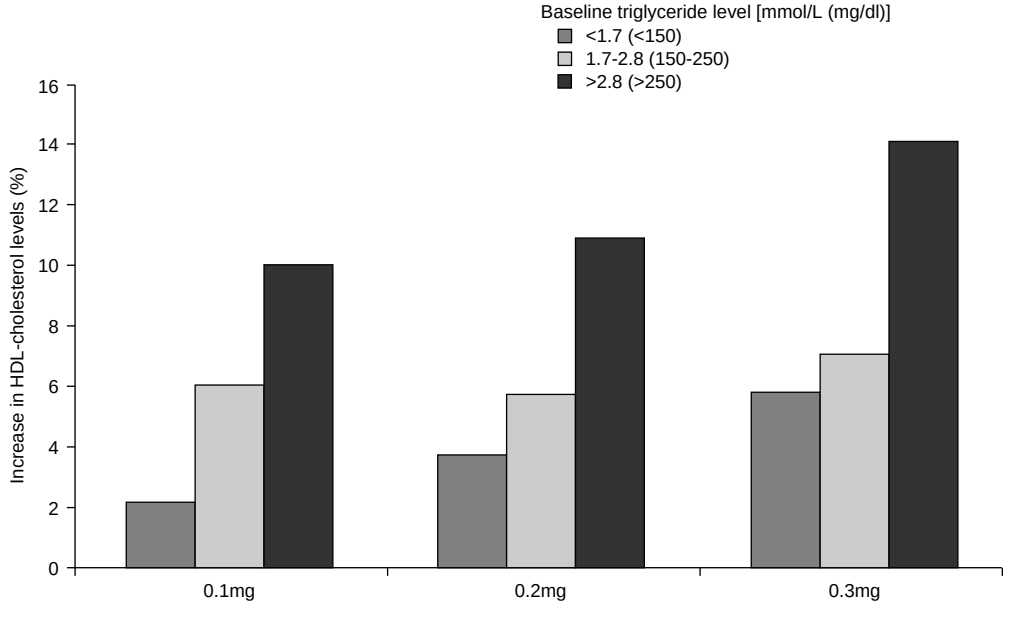

Fig. 4. Increase in high density lipoprotein (HDL)-cholesterol levels during 8 weeks' therapy with cerivastatin 0.1, 0.2 or 0.3 mg/day. Responses are stratified according to baseline triglyceride levels.[12]

titration study (n = 344).[15] Six weeks after the start of therapy, LDL-cholesterol reductions with cerivastatin 0.2 mg/day (–26.4%) were significantly greater than those seen with fluvastatin 20 mg/day (–19.3%; $p < 0.001$). After a further 6 weeks' treatment at higher dosages, cerivastatin 0.3 mg/day produced greater changes than fluvastatin 40 mg/day in LDL-cholesterol (–30.3 *vs* –23.6%), HDL-cholesterol (+9.3 *vs* +4.0%) and serum triglyceride levels (–14.1 *vs* –3.7%) [$p < 0.001$ for all comparisons].

2.1 Potency Versus Efficacy

The therapeutic potency of an HMG-CoA reductase inhibitor may be defined as *the amount of drug required to achieve a specific reduction in LDL-cholesterol attainable by all drugs in the class.* The potency of a drug is established early in phase II or III of development and does not change with further dosage extension studies. Without directly comparative studies, it is possible to establish relative potency by comparing the daily dose of the currently available HMG-CoA reductase inhibitors required to produce a mean 30% reduction in LDL-cholesterol levels. The approximate corresponding values with regard to the relative potency of these agents are presented in table I.

Another way of expressing potency is in terms of pharmacological potency, which is the amount of drug required to inhibit HMG-CoA-reductase activity *in vitro*. When cell membrane bound enzyme is used, cerivastatin produces 50% inhibition of HMG-CoA reductase at significantly lower concentrations than atorvastatin, simvastatin, fluvastatin, lovastatin and pravastatin.[21-23]

Table I. The relative potency of currently available HMG-CoA reductase inhibitors based on the daily dose required to achieve a mean 30% reduction in LDL-cholesterol levels

Drug	Daily dose (mg)	Relative potency[a]
Fluvastatin[16]	60	1
Pravastatin[17]	30	2
Lovastatin[18]	20	3
Simvastatin[19]	10	6
Atorvastatin[20]	5	12
Cerivastatin[6]	0.3	200

a Where potency of fluvastatin 60mg = 1.

Thus, cerivastatin – the first HMG-CoA reductase inhibitor with clinical activity at dosages of <1mg – is the most potent drug (pharmacologically and therapeutically) available in its class.

In contrast to potency, efficacy is dose and tolerability dependent. The efficacy of the HMG-CoA reductase inhibitors may be defined as *the maximum amount of LDL-cholesterol reduction achievable at the highest dose of the drug.* When the maximum daily dosage (either approved for general use or currently in clinical trials) is used, atorvastatin 80mg is the most efficacious agent, with LDL-cholesterol reductions of 54%, followed by simvastatin 80mg (47%), cerivastatin 0.8mg (44%) and lovastatin 80mg (40%).[13,20,24]

3. Tolerability

Cerivastatin is generally well tolerated. In pooled tolerability data from placebo or comparator controlled trials,[25] no significant difference in the incidence of adverse events was detected between

Table II. Effect of cerivastatin on plasma fibrinogen levels[15]

	No. of patients	Fibrinogen level (g/L)[a]		Change from baseline[b]	
		baseline	week 8	absolute	percentage
Placebo	108	2.68	2.68	0.003	0.7
Cerivastatin 0.1 mg/day	102	2.77	2..76	-0.006	1.0
Cerivastatin 0.2 mg/day	117	2.69	2.71	0.024	2.2
Cerivastatin 0.3 mg/day	108	2.73	2.77	0.038	2.2

a To convert to mg/dl, multiply by 100.

b For all reported changes, $p > 0.05$.

recipients of cerivastatin 0.2 or 0.3 mg/day (n = 1394) and placebo recipients (n = 641). The incidence of drug-related withdrawals with cerivastatin (0.1 to 0.4 mg/day) [1.6%] was at least comparable to that seen with placebo (2.2%) or other HMG-CoA reductase inhibitors (3.2%) in 3460 patients evaluated in clinical studies.[25]

During cerivastatin therapy, elevations in levels of hepatic transaminases (ALT and AST) and creatine kinase were rare and not related to dose.[25] In general, the incidence of hepatic enzyme elevations observed with cerivastatin was similar to that observed with other HMG-CoA reductase inhibitors and placebo. Similarly, absolute or percentage changes in fibrinogen levels after 8 weeks of cerivastatin therapy or placebo were minor and not significantly different (table II).[15]

4. Summary

Cerivastatin is a third generation HMG-CoA reductase inhibitor, the most potent drug in its class, and the first to be available in daily doses of <1mg. Clinical trials with the 0.8 mg/day dosage indicate that cerivastatin has the potential to rank among the most efficacious agents. It effectively reduces total and LDL-cholesterol and triglyceride levels and increases levels of HDL-cholesterol. On the basis of its demonstrated clinical efficacy and safety, cerivastatin is a suitable choice of lipid-lowering agent for most patients with hypercholesterolaemia.

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