CLINICAL STUDIES

Effectiveness of Statin-Gemfibrozil Combination Therapy in Patients With Mixed Hyperlipidemia: Experience of a Community Lipid Clinic and Safety Review From the Literature

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This retrospective study was carried out to assess the effectiveness of statin-gemfibrozil combination therapy in a community practice lipid clinic and to review safety data from published literature. Forty-six consecutive patients received a statin and gemfibrozil combination for resistant hyperlipidemia to either agent therapy. Fasting total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), and triglycerides (mg/dL) were measured. Low-density lipoprotein cholesterol (mg/dL) was calculated using the Friedewald formula if triglycerides were <400 mg/dL. Combination therapy reduced total cholesterol, low-density lipoprotein cholesterol, and triglycerides by 11% (p=0.02), 22% (p=0.049), and 39% (p=0.0002), respectively, and raised high-density lipoprotein cholesterol by 5% (p=0.3). A pooled analysis of 838 patients from the literature on statin-gemfibrozil combination therapy revealed an incidence of myositis and severe myopathy of 0.7% and 0.6%, respectively (excluding cerivastatin). We conclude that statin-gemfibrozil combination therapy is effective in significantly reducing total cholesterol, low-density lipoprotein cholesterol, and triglycerides with a trend toward raising high-density lipoprotein cholesterol in patients with hyperlipidemia resistant to either agent alone. Myositis and severe myopathy are infrequent, but not rare side effects which may be statin-specific regarding the incidence of occurrence. (Prev Cardiol. 2003;6:189–194)

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Desirable levels of lipids, particularly in patients with coronary artery disease, might not be achievable with single-agent lipid-lowering drugs. The recently updated American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention of coronary artery disease recommend a low-density lipoprotein cholesterol (LDL-C) of <100 mg/dL, a high-density lipoprotein cholesterol (HDL-C) of >40 mg/dL, and a triglyceride (TG) level of <150 mg/dL.[1] Statins (3-hydroxy-3-methylglutaryl coenzyme A inhibitors) are very effective agents in reducing LDL-C, modestly lowering TG, and increasing HDL-C, whereas fibric acid derivatives are mostly effective in reducing TG and increasing HDL-C.[2,3] In patients with mixed resistant hyperlipidemia, both statins and fibrates might be necessary to effectively lower TG and raise HDL-C to meet the new guidelines.

Small studies have suggested that the combination therapy of fibric acid derivatives and statins remains safe and effective in reducing total cholesterol (TC) and TG and increasing HDL-C.[2,3] Several case reports have shown, however, that a statin-gemfibrozil combination may have an increased incidence of severe myositis and rhabdomyolysis compared with monotherapy. These side effects have been reported with statins alone,[4–13] gemfibrozil alone,[14,15] and the combination of statins and gemfibrozil.[16–35]

In this study we evaluated the efficacy of adding a statin to gemfibrozil or gemfibrozil to a statin in altering TC, HDL-C, TG, and calculated LDL-C in patients with resistant hyperlipidemia in a private practice-based lipid clinic. The incidence of myositis

and severe myopathy was compiled from prospective studies published in the literature (excluding cerivastatin, which was recently pulled off the market).

METHODS

We retrospectively reviewed data on 46 consecutive patients in our lipid clinic who received a statin-gemfibrozil combination therapy for mixed resistant hyperlipidemia between May 1998 and April 2000. Resistant hyperlipidemia was defined as continued elevation of TC or TG above recommended guidelines for secondary prevention (TC >200 mg/dL and TG >150 mg/dL) despite the use of a statin or gemfibrozil alone. Twenty-four patients (group 1) were on a statin (atorvastatin, n=16; pravastatin, n=4; simvastatin, n=3; cerivastatin, n=1) before the addition of gemfibrozil. Twenty-two patients (group 2) were on gemfibrozil before the addition of a statin (atorvastatin, n=6; pravastatin, n=8; simvastatin, n=7; fluvastatin, n=1). Statins were utilized in the following dosing range: atorvastatin 10–40 mg, pravastatin 10–40 mg, simvastatin 5–40 mg, fluvastatin 40 mg, and cerivastatin 0.4 mg. Gemfibrozil was generally administered as 600 mg once or twice a day. Fasting TC, HDL-C, and TG were measured in the lipid clinic using the Cholestech L.D.X. machine (Cholestech Corp., Hayward, CA). Daily quality check of the machine was performed in the lipid clinic according to manufacturer recommendation. All patients were instructed by a nurse practitioner on a Step II AHA diet. LDL-C was calculated by using the Friedewald formula: LDL=TC-(HDL+TG/5) if TG levels were <400 mg/dL.[36] When TG values were ≥400 mg/dL, only TC values were included in the analysis.

The following variables were collected for both groups 1 and 2: gender, age, history of hypertension, presence of diabetes mellitus, and length of time on the combination therapy. Serum creatinine kinase (CK) was not measured routinely and only if a patient complained of significant myalgia or muscle weakness. Data on TC (mg/dL), TG (mg/dL), HDL-C (mg/dL), calculated LDL-C (mg/dL), and TC/HDL-C were collected when patients were on monotherapy with either a statin or gemfibrozil and after ≥3 months of combination therapy. Baseline lipid values before any treatment were incomplete because many patients were referred to our clinic already initiated on a statin or gemfibrozil. Patients with pre-existing renal insufficiency or taking more than a statin-gemfibrozil combination to lower their cholesterol were excluded from this analysis.

Statistical Analysis

Paired *t* test was performed to compare differences between TC, TG, LDL-C, TC/HDL-C, and HDL-C before and after combination treatment in the same group. Nonpaired *t* test and chi-square test were performed to compare continuous and dichotomous variables, respectively, between group 1 and group 2. A *p* value of <0.05 was considered statistically significant.

Review of the Literature

Using The National Library of Medicine bibliographic database MEDLINE, prospective published series on the frequency of severe myopathy and myositis with statin-gemfibrozil combination therapy were reviewed. The following keywords were used for the MEDLINE search: gemfibrozil, gemfibrozil and myopathy, gemfibrozil and myositis, myositis and statin, myopathy and statin, statin and fibrate, rhabdomyolysis and gemfibrozil, lovastatin and gemfibrozil, atorvastatin and gemfibrozil, pravastatin and gemfibrozil, simvastatin and gemfibrozil, fluvastatin and gemfibrozil, lovastatin and rhabdomyolysis, simvastatin and rhabdomyolysis, pravastatin and rhabdomyolysis, fluvastatin and rhabdomyolysis, and atorvastatin and rhabdomyolysis.

The incidence of these events was determined for each statin alone and for all of the statins combined. Severe myopathy was defined as a rise of CK >10,000 IU/L from baseline (or >10 times the baseline value). Myositis was defined as abnormal CK rise ≥3 times above pretreatment level, but <10,000 IU/L (or <10 times baseline value) with or without muscle weakness or pain.

RESULTS

Descriptive analysis is shown in Table I. There was no statistical difference between groups 1 and 2 with respect to age, gender, or the length of time of therapy with statin-gemfibrozil combination compared with each drug alone. Diabetes mellitus and hypertension appeared to be more prevalent in group 1 than in group 2, but statistical significance was not reached.

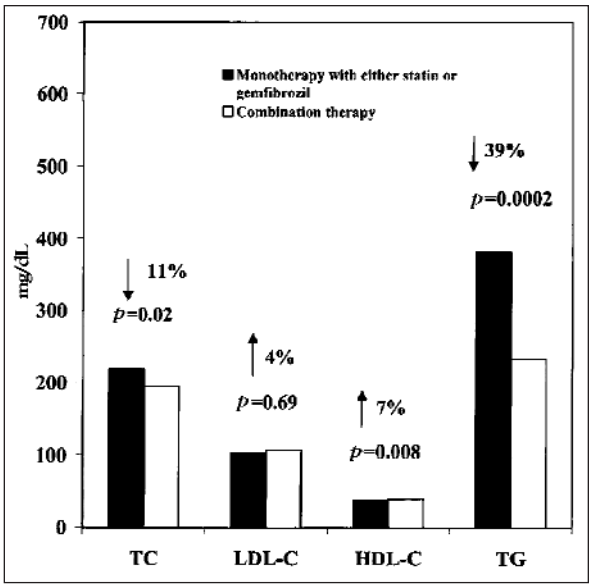

Figure. Effect of statin-gemfibrozil combination compared with either therapy alone on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C), and triglyceride (TG)

Effectiveness of Combination Therapy

Table II illustrates the effect of gemfibrozil-statin combination therapy on lipid levels compared with monotherapy alone. Gemfibrozil added to a statin significantly lowered TG (-40.6) but did not significantly increase LDL-C or HDL-C, whereas a statin added to gemfibrozil significantly lowered TC (-17%), LDL-C (-32.9%), and TG (-36.1%) but had no significant effect on HDL-C. When all patients are considered, statin-gemfibrozil combination significantly lowered TC (-11%), TG (- 38.9%), and LDL-C (-22%) with a trend toward increasing HDL-C (+5%) when compared with monotherapy alone (Figure).

Myositis and Myopathy With Statin-Gemfibrozil Combination Therapy

One case of severe rhabdomyolysis occurred in the only patient treated with cerivastatin-gemfibrozil combination. Myalgia was reported in four patients following initiation of combination therapy. CK was obtained in two of the four patients and levels were normal. The other two patients discontinued their treatment before any CK enzymes were obtained. Myalgia resolved upon discontinuation of the statin-gemfibrozil combination in all four patients.

Table III illustrates a summary of published prospective series from which the rate of severe myopathy and myositis in patients on both statins and gemfibrozil was possible to calculate. The percent of patients who developed severe myopathy and myositis were 0.6% and 0.7%, respectively. Lovastatin-gemfibrozil combination had a higher incidence of severe myopathy and myositis of 3.9% and 4.5%, respectively. The incidence of myositis could have been underestimated because CK measurements were not routinely obtained for patients with no complaints of myalgia. Pravastatin had the greatest number of published reports and showed no rhabdomyolysis when combined with gemfibrozil but an approximate 1% incidence of myosi-

Table I. Descriptive Analysis

	Group 1 (n=24)	Group 2 (n=22)	Groups 1&2 (n=46)	*p* Value*
Age (years)**	65.4±10.1	64±10.9	64.7±10.4	0.67
Gender (% male)	61	68	64	0.75
Diabetes mellitus (%)	48	23	36	0.92
Hypertension (%)	52	41	47	0.08
Treatment time with combination (months)**	13.8±10.7	12.7±10.1	13.2±10.3	0.73

**p* value between group 1 and group 2; **mean±SD

Table II. Total Cholesterol, Calculated LDL-C, HDL-C, Mean TC/HDL-C, and Triglyceride Level in Patients on Monotherapy and Combination Therapy with Statin-Gemfibrozil

	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	TC/ HDL-C
Monotherapy with statin	214.39±77.97	108.10±80.9	37.18±10.0	449.92±228.26	5.8
Combination gemfibrozil added to statin	204.91±57.17	112.80±31.90	41.82±6.5	267.21±204.80	4.9
Difference (combination–monotherapy)	-9.48	4.7	4.6	-182.71	-0.9
p Value	0.58	0.83	0.21	0.003	-
Monotherapy with gemfibrozil	221.96±26.76	136.49±31.81	39.72±8.3	307.96±226.90	5.6
Combination statin added to gemfibrozil	184.24±36.49	91.60±50.70	40.28±6.9	196.73±81.29	4.6
Difference (combination–monotherapy)	-37.72	-44.89	0.56	-111.23	-1
p Value	0.0002	0.002	0.83	0.02	-
Monotherapy with either statin or gemfibrozil	218.09±58.28	126.3±54.9	38.8±8.9	382.02±236.21	5.6
Combination therapy	195.05±49.00	99.16±45.46	40.9±6.7	233.50±160.59	4.8
Difference (combination–monotherapy)	-23.04	-27.14	2.1	-148.52	-0.8
p Value	0.02	0.049	0.3	0.0002	-

Numbers are mean±SD deviation; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; TC=total cholesterol

Table III. Summary of Published Series on Myositis and Severe Myopathy with Statin-Gemfibrozil Combination

Statin	N*	Gemfibrozil (mg)	Statin Dose (mg)	Myositis	Severe Myopathy**	Series Follow-Up	Reference
Pravastatin	75	600 b.i.d.	40 q.d.	3	0	12 weeks	Wiklund[31]
Pravastatin	135	600 b.i.d.	20 q.d.	0	0	≤4 years	Athyros[2]
Pravastatin	161	600 b.i.d.	mean 24.4 q.d.	0	0	mean 2.36 years	Murdock[3]
Pravastatin	14	600 b.i.d.	20 q.d.	?	0	24 months	Napoli[29]
Pravastatin	32	1200	10–40 q.d.	1	0	53 weeks	Rosenson[32]
Subtotal	**417**			**4 (1.0%)**	**0 (0%)**		
Simvastatin	130	600 b.i.d.	20 q.d.	0	0	≤4 years	Athyros[2]
Simvastatin	108	600 b.i.d.	mean 30.3 q.d.	0	1	mean 2.36 years	Murdock[3]
Subtotal	**238**			**0 (0%)**	**1 (0.4%)**		
Lovastatin	10	600 b.i.d.	mean 25 q.d.	0	0	mean 2.36 years	Murdock[3]
Lovastatin	12	600 b.i.d.	40 b.i.d.	1	0	≤3 months	Illingworth[28]
Lovastatin	80	?	20–80 q.d.	?	4	?	Tobert[34]
Subtotal	**102**			**1 (4.5%)**	**4 (3.9%)**		
Atorvastatin	30	600 b.i.d.	mean 14.3 q.d.	0	0	mean 2.36 years	Murdock[3]
Subtotal	**30**			**0 (0%)**	**0 (0%)**		
Fluvastatin	34	600 b.i.d.	mean 27.9 q.d.	0	0	mean 2.36 years	Murdock[3]
Fluvastatin	17	600 b.i.d.	20 b.i.d.	0	0	2 weeks	Spence[33]
Subtotal	**51**			**0 (0%)**	**0 (0%)**		
Total	**838**			**5 (0.7%)**	**5 (0.6%)**		

*N=patients on combination of statin and gemfibrozil; **severe myopathy is defined as a rise of creatine kinase (CK) >10,000 IU/L (or ≥10 times baseline value), myositis is defined as abnormal CK rise ≥3 times above pretreatment level but <10 times baseline value with or without muscle weakness or pain

tis. Although gemfibrozil combined with fluvastatin and atorvastatin showed no rhabdomyolysis, the published experience was too small to make any meaningful safety conclusions. Recently, cerivastatin has been pulled off the market because of a higher rate of severe myopathy. Cerivastatin was not included in our pooled data from the literature. The US Food and Drug Administration reporting rates of rhabdomyolysis with cerivastatin were 16–80 times higher than other statins. Even when cases of cerivastatin administration with gemfibrozil were excluded, rhabdomyolysis reporting rates were still 10–50 times higher than current statins on the market.[37]

CONCLUSION

In patients with combined hyperlipidemia, single-drug therapy often fails to lower TG and TC and raise HDL-C to the optimal levels set by the recent National Education Cholesterol Program and the ACC/AHA guidelines.[1] Statin-gemfibrozil combination therapy can be effective in achieving further lowering of TG, TC, and LDL-C and raising HDL-C above what monotherapy alone can achieve.[2,3,29–31] Similarly, in our study the addition of gemfibrozil to a statin yielded a significant drop in TG whereas the addition of a statin to gemfibrozil significantly reduced TC, TG, and LDL-C. The statin-gemfibrozil combination was superior to either monotherapy alone in reducing TC, LDL-C, and TG and in increasing HDL-C in patients with resistant hyperlipidemia.

The effect of the statin-gemfibrozil combination on LDL-C compared with untreated subjects could not be determined in our study because the majority of patients were already on either a statin or gemfibrozil when referred to our lipid clinic. Iliadis and Rosenson[35] found a 14% drop in LDL-C in mixed hyperlipidemia patients treated with gemfibrozil and pravastatin compared with untreated patients ($p=0.24$). Furthermore, Athyros et al.[2] showed an LDL-C reduction of 35% and 39% in patients with familial combined hyperlipidemia treated with pravastatin-gemfibrozil (n=135) and simvastatin-gemfibrozil (n=130), respectively, compared with baseline. In our study, statin-gemfibrozil combination significantly reduced LDL-C by 22% above monotherapy alone.

Several case reports have indicated that myositis and rhabdomyolysis do occur with combination

therapy. The incidence of these complications is not well defined. It is known, however, that myopathy due to gemfibrozil alone or statin alone is very low. It is estimated that 0.2% of patients develop severe myopathy with lovastatin alone and up to 5% with the combination of lovastatin and gemfibrozil.[34] In pooled data from the literature (Table III), severe myopathy occurred in 0.4% with simvastatin-gemfibrozil and in 3.9% with lovastatin-gemfibrozil combination. Severe myopathy did occur in the only patient in our cohort who received cerivastatin-gemfibrozil combination. There is a lack of substantial published data on fluvastatin and atorvastatin combination with gemfibrozil (Table III). In contrast, severe myopathy was not seen in 417 patients on pravastatin-gemfibrozil in our pooled analysis. Recent data published in abstract form also suggest that fluvastatin-gemfibrozil combination has good tolerability and is associated with a low myopathic risk.[38] These findings suggest a statin-specific interaction with gemfibrozil that may not be a "class effect."

Although no randomized, controlled trials have been conducted on the safety and efficacy of statin-gemfibrozil combination among different statins, it is possible that certain statins might have a safer profile than others when combination therapy is initiated. Igel et al.[39] noted that statins that lack a significant hepatic metabolism (like pravastatin), that are metabolized by more than one cytochrome P450 isoenzyme (like fluvastatin), or that are metabolized by other cytochrome P450 isoenzymes in case of blockage of the main metabolizing enzyme (like cerivastatin) might have the least drug-to-drug interactions. However, despite a dual hepatic pathway to metabolize cerivastatin, this statin continued to have a higher incidence of myopathy and had to be withdrawn from the market. Furthermore, statins have substantial differences as immuno-modulators[40] and in their ability to alter collagen content and smooth muscle cell accumulation in atheromas.[41,42] It is important, irrespective of the statin utilized, to closely monitor CK enzymes in patients on statin-gemfibrozil combination to detect early myositis. Patients should be instructed on the signs and symptoms of myalgia and myopathy and they should report any of these findings to their physician. After performing this review, we changed the protocol in our lipid clinic to allow routine CK checks on patients receiving statin-gemfibrozil combination therapy.

Statin-gemfibrozil combination therapy has a very infrequent but not rare incidence of severe myopathy and rhabdomyolysis as seen in the pooled data from published smaller, randomized trials. We are not aware of similar pooled analysis in the literature. The combination therapy seems, however, to be effective in lowering TC, LDL-C, and TG and raising HDL-C when compared with monotherapy alone and might be necessary to achieve optimal lipid levels in high-risk patients with combined hyperlipidemia. Careful patient education about the potential side effects of statins in general and statin-gemfibrozil combination in specific is essential to detect early myositis and hopefully prevent progression to severe myopathy or rhabdomyolysis.

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References

1 Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death with atherosclerotic cardiovascular disease: 2001 update. *J Am Coll Cardiol.* 2001;38:1581–1583.
2 Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol.* 1997;80:608–613.
3 Murdock DK, Murdock AK, Murdock RW, et al. Long-term safety and efficacy of combination gemfibrozil and HMG-CoA reductase inhibitors for the treatment of mixed lipid disorders. *Am Heart J.* 1999;138:151–155.
4 Wallace CS, Mueller BA. Lovastatin-induced rhabdomyolysis in the absence of concomitant drugs. *Ann Pharmacother.* 1992;26(2):190–192.
5 Sylvain-Moore H, Worden JP Jr. Lovastatin-associated rhabdomyolysis. *Heart Lung.* 1991;20(5 pt 1):464–466.
6 Chu PH, Chen WJ, Chiang CW, et al. Rhabdomyolysis, acute renal failure and hepatopathy induced by lovastatin monotherapy. *Jpn Heart J.* 1997;38(4):541–545.
7 Manoukian AA, Bhagavan NV, Hayashi T, et al. Rhabdomyolysis secondary to lovastatin therapy. *Clin Chem.* 1990;36(12):2145–2147.
8 Deslypere JP, Vermeulen A. Rhabdomyolysis and simvastatin. *Ann Intern Med.* 1991;114(4):342.
9 Berland Y, Vacher Coponat H, Durand C, et al. Rhabdomyolysis with simvastatin use. *Nephron.* 1991; 57(3):365–366.
10 Bizzaro N, Bagolin E, Milani L, et al. Massive rhabdomyolysis and simvastatin. *Clin Chem.* 1992;38(8 pt 1):1504.
11 Ucar M, Mjorndal T, Dhalqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Saf.* 2000;22(6):441–457.
12 Rodriguez ML, Mora C, Navarro JF. Cerivastatin-induced rhabdomyolysis. *Ann Intern Med.* 2000;132(7):598.
13 Kogan AD, Orenstein S. Lovastatin-induced acute rhabdomyolysis. *Postgrad Med J.* 1990;66:294–296.
14 Gorriz JL, Sancho A, Lopez-Martin JM, et al. Rhabdomyolysis and acute renal failure associated with gemfibrozil therapy. *Nephron.* 1996;74(2):437–438.
15 Magarian GJ, Lucas LM, Colley C. Gemfibrozil-induced myopathy. *Arch Intern Med.* 1991;151(9):1873–1874.
16 Duell PB, Connor WE, Illingworth DR. Rhabdomyolysis after taking atorvastatin with gemfibrizol. *Am J Cardiol.* 1998; 81(3):368–369.
17 Pogson GW, Kindred LH, Carper BG. Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrizol combination therapy. *Am J Cardiol.* 1999;83(7):1146.
18 Bermingham RP, Whitsitt TB, Smart ML, et al. Rhabdomyolysis in a patient receiving the combination of cerivastatin and gemfibrizol. *Am J Health Syst Pharm.* 2000;57(5):461–464.
19 Alexandridis G, Pappas GA, Elisaf MS. Rhabdomyolysis due to combination therapy with cerivastatin and gemfibrizol. *Am J Med.* 2000;109(3):261–262.
20 Ozdemir O, Boran M, Gokce V, et al. A case with severe rhabdomyolysis and renal failure associated with cerivastatin-gemfibrizol combination therapy—a case report. *Angiology.* 2000;51(8):695–697.
21 Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination. *JAMA.* 1990;264(1):71–75.

22 Goldstein MR. Myopathy and rhabdomyolysis with lovastatin taken with gemfibrozil. *JAMA.* 1990;264(23):2991–2992.
23 Abdul-Ghaffar N, El-Sonbaty MR. Pancreatitis and rhabdomyolysis associated with lovastatin-gemfibrozil therapy. *J Clin Gastroenterol.* 1995;21(4):340–341.
24 Glueck CJ, Oakes N, Speirs J, et al. Gemfibrozil-lovastatin therapy for primary hyperlipoproteinemias. *Am J Cardiol.* 1992;70:1–9.
25 Marais GE, Larson KK. Rhabdomyolysis and acute renal failure induced by combination lovastatin and Gemfibrozil therapy. *Ann Intern Med.* 1990;112(3):228–230.
26 Van Puijenbroek EP, Du Buf-Vereijken PW, Spooren PF, et al. Possible increased risk of rhabdomyolysis during concomitant use of simvastatin and gemfibrozil. *J Intern Med.* 1996; 240(6):403–404.
27 Tal A, Rajeshhawari M, Isley W. Rhabdomyolysis associated with simvastatin-gemfibrozil therapy. *South Med J.* 1997; 90(5):546–547.
28 Illingworth DR, Bacon S. Influence of lovastatin plus gemfibrozil on plasma lipids and lipoproteins in patients with heterozygous familial hypercholesterolemia. *Circulation.* 1989; 79:590–596.
29 Napoli C, Lepore S, Chiariello P, et al. Long term treatment with pravastatin alone and in combination with gemfibrozil in familial type IIB hyperlipoproteinemia or combined hyperlipidemia. *J Cardiovasc Pharmacol Ther.* 1997;2(1):17–26.
30 Pasternak RC, Brown LE, Stone PH, et al., for the Harvard Atherosclerosis Reversibility Project (HARP) Study Group. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. *Ann Intern Med.* 1996;125:529–540.
31 Wiklund O, Bergman M, Bondjers G, et al. Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. *Am J Med.* 1993;94(1):13–20.
32 Rosenson RS, Frauenheim WA. Safety of combined pravastatin-gemfibrozil therapy. *Am J Cardiol.* 1994;74:499–500.
33 Spence JD, Munoz CE, Hendricks L, et al. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. *Am J Cardiol.* 1995;76:80A–83A.
34 Tobert JA. Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation [letter]. *N Engl J Med.* 1988; 318(1):47–48.
35 Iliadis EA, Rosenson RS. Long-term safety of pravastatin-gemfibrozil therapy in mixed hyperlipidemia. *Clin Cardiol.* 1999;22:25–28.
36 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499–502.
37 Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation.* 2002;106:1024–1028.
38 Statins are not all alike: study reveals no increased risk of musculoskletal effects. From data presented at the XIV International Symposium on Drugs Affecting lipid Metabolism (DALM), *MediView Express Report*. September 9–12, 2001.
39 Igel M, Sudhop T, Bergmann K. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins). *Eur J Clin Pharmacol.* 2001;57:357–364.
40 Kwak B, Mulhaupt F, Myit S, et al. Statins as a newly recognized type of immunomodulator. *Nat Med.* 2000;6:1399–1402.
41 Fukumoto Y, Libby P, Rabkin E, et al. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of Watanabe heritable hyperlipidemic rabbits. *Circulation.* 2001;103(7):993–999.
42 Shiomi M, Ito T, Hirouchi Y, et al. Fibromuscular cap composition is important for the stability of established atherosclerotic plaques in mature WHHL rabbits treated with statins. *Atherosclerosis.* 2001;157:75–84.