DRUG USE REVIEW
NEWSLETTER

Vol. 8, No. 6
October/November 2003

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STATIN THERAPY

Introduction

Cardiovascular disease is the leading cause of death for men and women in the United States. Elevated low-density lipoprotein cholesterol (LDL-C) and lowered high-density lipoprotein (HDL-C) are major risk factors for developing cardiovascular disease. Over 100 million Americans have total cholesterol levels above the desired level (200 mg/dL).[1] There is an increased awareness in the United States concerning the risks associated with cardiovascular disease and a great emphasis placed on preventing these diseases and its associated mortality.
Discussion of hypercholesterolemia and target cholesterol levels is beyond the scope of this newsletter, however more information may be found in the National Cholesterol Education Program (NCEP) guidelines at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm. Several drug classes have been proven effective in lowering cholesterol levels and decreasing mortality associated with cardiovascular events. The focus of this newsletter will be Statin Therapy.

Statins (HMG-CoA Reductase Inhibitors)

These agents work by inhibiting HMG-CoA reductase, causing upregulation of the LDL-C receptors on the surface of the liver and increasing the removal of LDL-C from the blood. LDL-C lowering appears to play a major role in decreasing the risk of coronary heart disease (CHD) and all-cause mortality.[2] Beyond LDL-C lowering, the statins also lower triglycerides and modify endothelial function, inflammatory responses, plaque stability, and thrombus formation, in addition to being relatively well tolerated.[3] Primary and secondary CHD prevention studies have shown the overall long-term benefit of various statins.[4]

Six agents are currently available in this class. All are unique in structure, pharmacokinetics, and pharmacologic potency. Current evidence does not show an absolute advantage of one product over another. However, there is a difference in LDL-C lowering efficacy when comparing agents on an mg per mg basis. One should note that in most cases, similar reductions in LDL-C between agents are obtainable when dosing is altered. (*see Appendix A*) Table 1 below lists available statins, strengths, dosage regimens, and respective lipid lowering ability.

General Information[5]

- Compliance with a prescribed diet should be followed in addition to statin therapy.
- Drug interactions occur when statins are taken with a number of other drugs including anticoagulants, bile acid resins, fibrates, immunosuppressive agents, niacin, azole antifungals, some HIV drugs and macrolide antibiotics.
- Patients should be advised to report any muscle weakness, discomfort, or brown urine immediately.

Monitoring[6]

- Follow-up visits every 6-8 weeks until treatment goal(s) are reached. Once goals are achieved, follow-up intervals may be reduced to every 4-6 months.
- Once treatment goal(s) are reached, lipoprotein profiles should be assessed preferably at each clinic visit, but at least annually.
- CK levels should be obtained initially and when muscle soreness, tenderness, or pain presents. Muscle symptoms should be evaluated at each visit.
- Evaluate liver function (ALT/AST) initially, approximately 12 weeks after starting, then annually or more frequently if indicated.

Safety[7]

All agents are well tolerated by most persons.

- *Elevated hepatic transaminases* are seen in 0.5% to 2% of cases and are dose dependent. It has not been determined whether this elevation correlates with true hepatotoxicity. Progression to liver failure is rare. Reversal of liver enzyme elevation is noted with a reduction in dose, and the increase is generally not seen to recur with re-challenge or selection of another statin. Though cholestasis and active liver disease are listed as contraindications to statin use, no specific evidence exists to show exacerbation of liver disease.
- Statins' ability to produce *myopathy* is well established, especially when used in combination with other antihyperlipidemia medications. Severe *myositis*, which involves muscle aches, soreness or weakness, and elevated creatine kinase levels (> 10 times normal), is rare in those prescribed statin monotherapy. In this case, drug therapy should be discontinued to prevent progression to rhabdomyolysis, myoglobinuria, or acute renal necrosis.
- Statins are *contraindicated* in pregnancy and lactation.

Table 1: Lipid Lowering Dose Ranges[8]

Drug	Strength	Dose	% ↓LDL-C	% ↑HDL-C	%↓Trigs	% ↓TC
Lovastatin*	10 mg	10 mg QD	22%	4%	5%	12%
	20 mg	20 mg QD	29%	7%	12%	21%
	40 mg	40 mg QD	31%	5%	2%	23%
	80 mg	40 mg BID	48%	8%	13%	36%
Atorvastati	10 mg	10 mg QD	38%	6%	13%	28%
	20 mg	20 mg QD	46%	5%	20%	35%
	40 mg	40 mg QD	51%	5%	32%	40%
	80 mg	80 mg QD	54%	1%	25%	42%
Fluvastatin	20 mg	20 mg QD	17%	1%	5%	13%
	40 mg	40 mg QD	23%	3%	13%	19%
	80 mg XL	80 mg QD	35%	8%	11%	20%
Pravastatin	10 mg	10 mg QD	19%	10%	3%	13%
	20 mg	20 mg QD	24%	3%	15%	18%
	40 mg	40 mg QD	34%	6%	10%	24%
Rosuvasta	5 mg	5 mg QD	45%	13%	35%	33%
	10 mg	10 mg QD	52%	14%	10%	36%
	20 mg	20 mg QD	55%	8%	23%	40%
	40 mg	40 mg QD	63%	10%	28%	46%
Simvastati	5 mg	5 mg QD	24%	7%	12%	17%
	10 mg	10 mg QD	28%	7%	12%	21%
	20 mg	20 mg QD	35%	5%	17%	26%
	40 mg	40 mg QD	41%	10%	15%	30%
	80 mg	80 mg QD	47%	12%	36%	36%

*MO Medicaid reference drug

Summary of Differences between Statins [3]

Lovastatin

- *Additional Dosing Information*
  - Should be taken with meals to maximize absorption
  - Doses can be taken as a single dose or as divided doses with meals
  - For patients taking concurrent immunosuppressive agents, it is recommended that lovastatin is initiated at 10 mg daily and does not exceed 20 mg daily
  - For patients with severe renal insufficiency (CLcr < 30ml per minute), doses above 20 mg daily should be carefully considered with cautious dose titration
  - After withdrawal of continuous therapy, duration of action continues for 4-6 weeks
- *Cardiac Benefits*
  - The **AFCAPS/TexCAPS** study noted a significant reduction in the risk for the first acute major coronary event, including non-fatal myocardial infarction (MI), unstable angina, and sudden cardiac death, in patients with average total cholesterol and LDL-C and below average HDL-C given 20-40 mg of lovastatin daily.[9]

Atorvastatin

- *Precautions*
  - Antacids may decrease plasma concentrations
  - Use with oral contraceptives may increase the hormones' duration of action
  - May elevate serum digoxin levels

    - Grapefruit juice in large amounts (> 1 quart per day) has been shown to elevate serum concentrations and increase area under the curve, therefore, increasing the possibility of myopathy.
- *Cardiac Benefits*
    - The **ASCOT-LLA** study showed a 36% reduction in fatal CHD and non-fatal MI in patients with average cholesterol levels given 10 mg of atorvastatin.[10]

Fluvastatin

- *Additional Dosing Information*
    - A 40 mg daily dose may be split and taken twice a day
- *Precautions*
    - May elevate serum digoxin levels
    - Cimetidine, omeprazole, and ranitidine taken with fluvastatin cause an increase in peak plasma concentrations and a decrease in clearance
    - Concurrent use of rifampin decreases serum rifampin concentrations and increases clearance of rifampin.
- *Cardiac Benefits*
    - The **LCAS** (Lipoprotein and Coronary Atherosclerosis Study) showed that fluvastatin slowed the progression of coronary atherosclerosis. Compared to placebo, fluvastatin significantly slowed the progression of lesions as measured by within-patient-per-lesion change in minimum lumen diameter. The primary endpoint was the percent of diameter stenosis and the formation of new lesions (13% of all fluvastatin versus 22% of all placebo patients). [19]

Pravastatin

- *Additional Dosing Information*
    - An initial dose of 10 mg once daily is recommended in patients with significant renal function impairment
    - An initial dose of 10 mg once daily is recommended for those with hepatic impairment and in the elderly population
    - In the elderly, maintenance doses of 20 mg daily or less are usually effective
- *Cardiac Benefits*
    - The **LIPID** study showed a 24% reduction in death from CHD, 22% reduction in overall mortality, and a significantly lower number of cardiovascular events in those patients given pravastatin 40 mg daily.[11] Positive results associated with primary prevention were confirmed for pravastatin in the **WOSCOPS** trial.[12]

Rosuvastatin

- *Additional Dosing Information*
    - No modification of dosage is necessary for patients with mild to moderate renal insufficiency (CLcr $\geq$ 30ml/min/1.73m^2). [17]
    - Dosing of rosuvastatin should be started at 5 mg once daily and not exceed 10 mg once daily in patients with severe renal impairment (CLcr < 30mL/min/1.73m^2) not on hemodialysis.[17]
    - Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin resulted in a decrease in plasma concentration of rosuvastatin by 54%. However, when the antacid is given 2 hours after rosuvastatin, there are no clinically significant changes on plasma concentrations of rosuvastatin.
    - If rosuvastatin is used in combination with gemfibrozil, the dose of rosuvastatin should be limited to 10 mg once daily.[17]
    - ~ 10% of rosuvastatin is metabolized by the P450 2C9 enzyme system.[17]

- *Precautions*
    - Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). When prescribing rosuvastatin and warfarin together, determine baseline INR prior to starting rosuvastatin, and monitor frequently to ensure that no significant alterations of INR occur.[17]
    - Consider dosing modification when prescribing rosuvastatin for patients of Japanese and Chinese descent, due to a 2-fold elevation in median exposure.[17]
- *Cardiac Benefits*
    - Lipid and apolipoprotein ratios have been shown to be strongly associated with CAD risk in previous studies. Pooled-data analysis showed that 12 weeks of rosuvastatin 10 mg resulted in clinically important reductions in lipid ratios that were significantly greater than those resulting from the treatment with the usual starting dose of atorvastatin, simvastatin, or pravastatin.[20]

Simvastatin

- *Additional Dosing Information*
    - For patients taking concurrent immunosuppressive agents, it is recommended that simvastatin is initiated at 5 mg daily and does not exceed 10 mg daily
    - For patients with severe renal insufficiency, begin therapy with 5 mg daily and monitor closely
- *Precautions*
    - May elevate serum digoxin levels
    - Large amounts of grapefruit juice (> 1 quart per day) reported to significantly increase serum concentrations, increasing myopathy risk
    - Protease inhibitors, nefazodone and amiodarone increase risk for rhabdomyolysis
    - Concurrent use with verapamil may increase risk of myopathy
- *Cardiac Benefits*[20]
    - The **Heart Protection Study** demonstrated a 25% reduction in the first event rate for major coronary events, stroke, and revascularizations in patients given simvastatin 40 mg daily.[13] A significant reduction in all case mortality for primary prevention was shown with simvastatin in the **4S** trial.[14]

What's New in Hypercholesterolemia therapy?

ZETIA® (ezetimibe) 10mg[15]

- First of a new class of lipid-lowering agents, **2-Azetidinones,** FDA approved 10/25/2002
- *Monotherapy:*
    - Lowers LDL-C approximately 18% as monotherapy
    - Monotherapy is an option for those patients with some contraindication to taking statins, but its novel use is directed toward combination therapy with statins.
- *ZETIA Initiated Concurrently with an HMG-CoA Reductase Inhibitor*
    - Lowered mean LDL-C levels by **additional 25% over statin alone**, when added concurrently with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin therapy. LDL-C reductions induced by ZETIA were generally consistent across all included statins.

    - Combination therapy may be utilized when:
        - Goal LDL-C concentrations not achieved with maximum statin doses
          Intolerable side effects experienced with statin therapy

ALTOCOR® (extended-release lovastatin) [15]
- Approved by the FDA in June of 2002
- Reduction in LDL-C of 25-42% with doses ranging from 10-60 mg, increased HDL-C 3-8%, and decreased triglycerides 18-33%
- Allows lovastatin to be taken on an empty stomach therefore, increasing absorption.

ADVICOR® (combination product of Niacin extended-release and lovastatin) [15]
- Approved by the FDA in December of 2001
- Reduced mean LDL-C 45%, increased mean HDL-C 41%, and decreased mean triglyceride levels by 42%
- Decreased risk of flushing due to extended-release formulation of niacin.
- Increased risk of myopathy vs. lovastatin alone.[21]

PRAVIGARD PAC™ [Combination of pravastatin (Pravachol®) and buffered aspirin]
- Indicated in patients for whom treatment with both pravastatin and buffered aspirin is appropriate
- Indicated to reduce the occurrence of cardiovascular events, including death, myocardial infarction or stroke, in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease.

PITAVASTATIN™ [16]
- Pitavastatin is not FDA approved, but is in Phase III trials
- Pitavastatin has similar efficacy data to date as rosuvastatin.
- Pitavastatin is not metabolized by the p450 3A4 enzyme system, therefore is expected to show efficacy somewhat similar to rosuvastatin with fewer drug interactions.[17]

Please send comments and suggestions regarding this newsletter to Jayne Zemmer,DUR Coordinator, Division of Medical Services, P.O. Box 6500 Jefferson City, MO 65102-6500

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Appendix A

Statin Dose by Target LDL-C Reduction[8]

% LDL-C REDUCTION DESIRED	STATIN AND RECOMMENDED DOSE
25% and below	**Lovastatin 10 mg** Fluvastatin 20 mg – 40 mg Pravastatin 10 mg – 20 mg Simvastatin 5 mg
25% to 35%	**Lovastatin 20 mg – 40 mg** Fluvastatin 40 mg – 80 mg Pravastatin 20 mg – 40 mg Simvastatin 10 mg – 20 mg Atorvastatin 10 mg
35% to 45%	**Lovastatin 40 mg – 80 mg** Atorvastatin 10 mg – 20 mg Fluvastatin 80 mg Pravastatin 40 mg Rosuvastatin 5 mg Simvastatin 20 mg – 40 mg
45% and greater	**Lovastatin 80 mg** Atorvastatin 20 mg – 80 mg Simvastatin 40 mg – 80 mg Rosuvastatin 10 mg – 40 mg

FDA Approved Statins

atorvastatin (Lipitor®)
fluvastatin (Lescol®)
lovastatin (Mevacor® and various generics)
pravastatin (Pravachol®)
rosuvastatin (Crestor®)
simvastatin (Zocor®)

Lovastatin is the MO Medicaid reference drug for this class of agents.

NOTE: From this table you can see that there is a difference in the effectiveness to lower LDL-C when comparing agents on a mg per mg basis. However, note that you can obtain similar reductions in LDL-C between agents when dosing is altered to produce similar effects.

For example, if you wanted to reduce a patient's LDL-C cholesterol by approximately 35%, you could use the following regimens:

- **Lovastatin 40 mg**
- Atorvastatin 10 mg
- Fluvastatin 80 mg
- Pravastatin 40 mg
- Rosuvastatin 5 mg
- Simvastatin 20 mg

HMG-CoA Reductase Inhibitor Use

April 2003 to August 2003

TOTAL PAID CLAIMS

PRODUCT	Total Claims	Apr 2003	May 2003	Jun 2003	Jul 2003	Aug 2003
ATORVASTATIN CALCIUM	70,904	14,513	14,628	13,961	14,351	13,451
LOVASTATIN	34,585	5,422	6,201	6,816	7,808	8,338
SIMVASTATIN	30,001	6,075	6,137	5,868	6,134	5,787
PRAVASTATIN SODIUM	14,903	3,081	3,078	2,917	2,995	2,832
FLUVASTATIN SODIUM	3,374	698	695	663	664	654
LOVASTATIN/NIACIN	541	100	110	104	115	112
ROSUVASTATIN CALCIUM	0	0	0	0	0	0
TOTAL	154,308	29,889	30,849	30,329	32,067	31,174

TOTAL PAID AMOUNTS

PRODUCTS	Total Paid	Apr 2003	May 2003	Jun 2003	Jul 2003	Aug 2003
ATORVASTATIN CALCIUM	$6,217,068	$1,262,618	$1,274,584	$1,221,491	$1,263,926	$1,194,449
SIMVASTATIN	$3,587,990	$724,042	$733,961	$700,185	$734,366	$695,436
LOVASTATIN	$1,879,095	$213,347	$351,616	$386,713	$446,405	$481,014
PRAVASTATIN SODIUM	$1,627,007	$335,151	$333,120	$320,409	$327,463	$310,864
FLUVASTATIN SODIUM	$216,818	$44,588	$44,645	$42,410	$42,717	$42,458
LOVASTATIN/NIACIN	$35,192	$6,219	$6,868	$6,615	$7,595	$7,895
ROSUVASTATIN CALCIUM	$0	$0	$0	$0	$0	$0
	$13,563,170	$2,585,965	$2,744,794	$2,677,823	$2,822,472	$2,732,116

PAID AMOUNT PER CLAIM

ATORVASTATIN CALCIUM	$	87.68
SIMVASTATIN	$	119.60
LOVASTATIN	$	54.33
PRAVASTATIN SODIUM	$	109.17
FLUVASTATIN SODIUM	$	64.26
LOVASTATIN/NIACIN	$	65.05