Statins induced myopathy

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STATINS – INTRODUCTION

- Structural analogs of HMG –CoA REDUCTASE (3 hydroxy 3 methyl glutaryl coenzyme A) in the liver
- 1987 : first approved for the use in treatment of hypercholesterolemia
- Most effective agents for reducing plasma chol. level
- Benefit in prevention of primary and secondary CHD
- Reduce of mortality and morbidity
- Good tolerance

STATINS - GENERATIONS

First generation (40-80 mg/day)

lovastatin(mevacor- pro drug), simvastatin(zocor- pro drug), pravastatin(pravachol)

Second generation(10-20 mg/day)

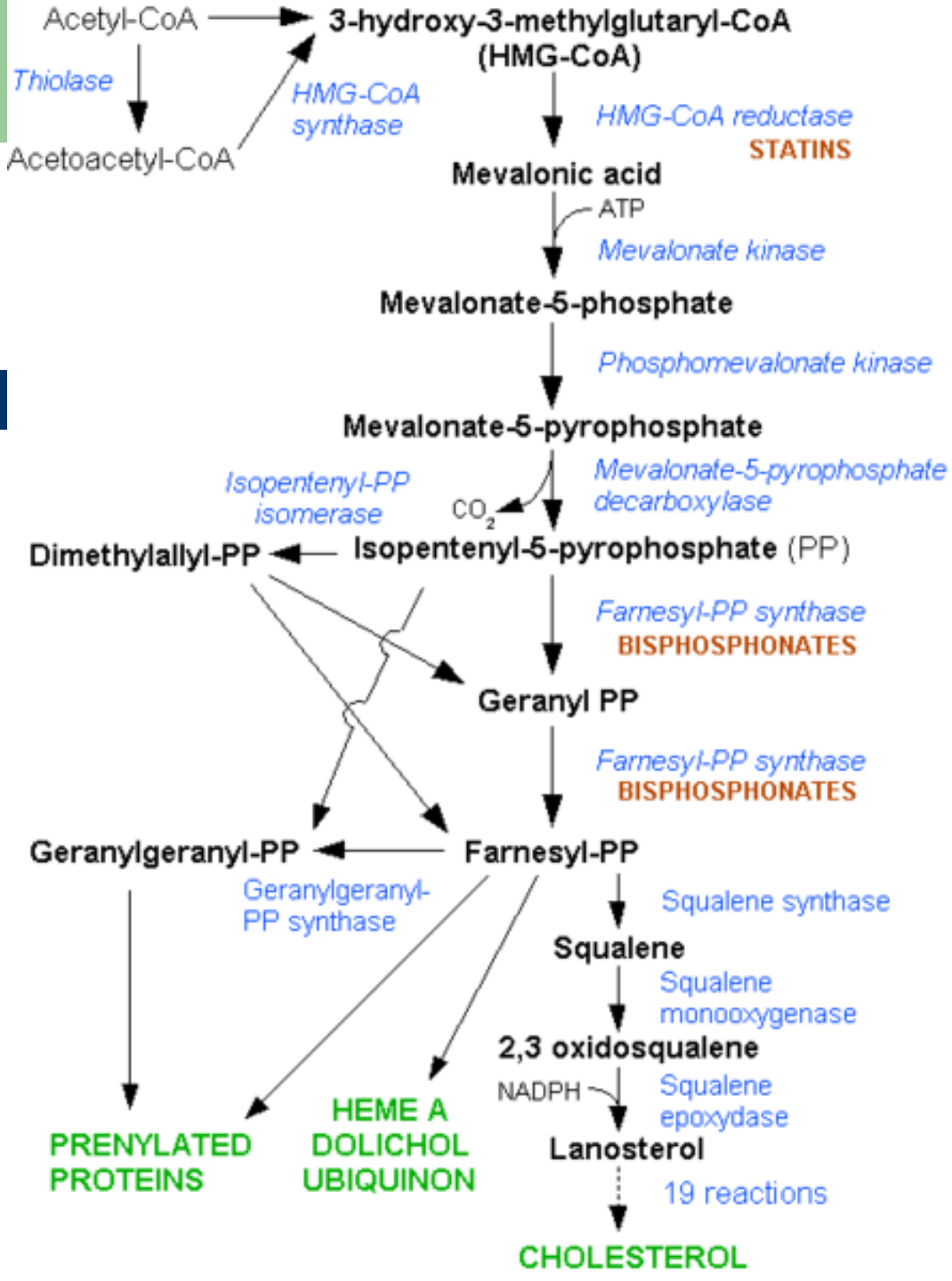
fluvastatin(lescol)

Third generation

atorvastatin(lipitor), cerivastatin(Baycol), rosuvastatin(crestor)

STATINS – MECHANISM OF ACTION

- HMG-CoA reductase mediates the first committed step in the chol. biosynthesis.
- Reversible binding
- The active forms of the reductase inhibitors are structural analogs of HMG-CoA intermediate that is the precursor of mevalonate
- Mevalonate is the precursor for cholesterol.
- Effect on other processes.


Acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
(HMG-CoA)
Thiolase
HMG-CoA
synthase
Acetoacetyl-CoA
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Isopentenyl-PP
isomerase
CO2
Mevalonate-5-pyrophosphate
decarboxylase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-
PP synthase
Squalene synthase
Squalene
Squalene
monooxygenase
2,3 oxidosqualene
NADPH
Squalene
epoxydase
Lanosterol
19 reactions
CHOLESTEROL
PRENYLATED
PROTEINS
HEME A
DOLICHOL
UBIQUINON

STATINS – EFFECTS

- Reduction of endogenous intracellular cholesterol leads to increase in gene expression of LDL-R.
- Increase hepatic uptake of LDL and its precursors such as IDL and VLDL.
- inhibit hepatic syntesis of apolipoprotein B-100
- Increase in apolipoprotein E receptor productions

STATINS – EFFECTS (cont.)

- inhibit hepatic syntesis of apolipoprotein B-100
- Increase in apolipoprotein E receptor productions
- Anti oxidation effect and inhibition of the scavenger receptors expression
- Improvement of endothel function (NO)
- reduce smooth muscle proliferation

STATINS – METABOLISM

- LIVER IS THE TARGET ORGAN
- METABOLISED BY THE CITOCHCROM P450 PATHWAY
- CYP2C9 – FLUVASTATIN
- CYP3A4 - ATORVASTATIN, LOVASTATIN, SIMVASTATIN
- Non p450 – PRAVASTATIN

Many drug interactions!

STATINS – ADVERSE EFFECT

- Myotoxic! -

  symptoms ranging from fatigue, weakness, and pain to symptoms associated with rhabdomyolysis.

- Constipation
- Flatulence
- Dyspepsia
- Nausea
- Gastrointestinal pain
- Peripheral neuropathy

STATINS - Mechanism of Statin-Induced myotoxicity

1. Depletion of secondary metabolic intermediates:

- ↓Mevalonate metabolite
- ↓Ubiquinone(CoQ10)

  lipid soluble electron carrier in membrane-bound electron transport chain of mitochondria (ATP) Mitochondrial dysfunction

- Instability and Disruption of plasma membrane
- Unstable action potential (Na/K channel)

STATINS - Mechanism of Statin-Induced myotoxicity (cont.)

2. Induction of apoptotic cell death:

(also pleiotropic benefits ! – tumor cells, cardiac hypertrophy)

Downstream isoprenoid moleules depletion leads → cytosolic calcium increase → BAX translocate into the mitochondria – release of cytochrome c → casp 9

→ casp 3 activation

STATINS - Mechanism of Statin-Induced myotoxicity (cont.)

3. Alteration of chloride channel conductance within the myocyte:

Simvastatin: ↓20% chloride conductance

block Cl channel→ muscle contraction → cramping/myalgia

Factors that increase the risk of a statin induced myopathy

Myotoxicity is dose dependant

Patient:

- Increased age, female sex, renal insufficiency, hepatic dysfunction, drug interactions.

Statin properties:

High systemic exposure, lipophilicity, high bioavailability, limited protein binding,

Potential for drug-drug interactions metabolized by CYP pathways (CYP3A4) !

STATINS – DRUG INTERACTIONS CYP3A4

Cyclosporin

Macrolide

SSRIs

CCB

Protease inhibitors

Azole anti fungal

Fibrate

- LOVASTATIN, SIMVASTATIN, ATORVASTATIN.

STATINS – DRUG INTERACTIONS CYP2C9

Azole anti fungal

Metronidazole

Amiadarone

Cimetidine

- FLUVASTATIN

STATINS – DRUG INTERACTIONS

NIACIN:

Nicotinic acid , vit B3.

FIBRATES:

- Potent TG lowering effect
- Some fibrateare metabolite by CYP3A4, CYP2C8

Gemfibrozilinteract with statin > other fibrate -

STATINS – CLINICAL RECOMMENDATION

- Before initiating statin: identify comorbid risk factors for develop myopathy
- Baseline CK measurement in whom prescribed statin (and then every 6-12 month) – if signs of myopathy measure.
- Statin therapy should be initiate in low dose
- Patient education

AHA/ACC/NHLBI clinical recommendations for statin myotoxicity

	CK levels	Clinical recommendations
Symptomatic patient	>10 Times normal	Discontinuation of statin therapy
	Normal levels or moderate elevation (3–10 times normal)	Follow-up of patient's symptoms and CK weekly
	Progressive CK elevation on serial measurements	Decrease in statin dose or temporary discontinuation of statin therapy
Asymptomatic patient	>10 Times normal	Strong consideration of discontinuing statin therapy
	Moderate elevation (3–10 times normal)	Patients can usually continue treatment with no harm Frequent and careful monitoring of symptoms and CK

THANK YOU FOR YOUR ATTENTION