Statins in chronic liver disease

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Summary

Statins are drugs widely used worldwide to treat hypercholesterolemia reducing cardiovascular risk. Clinical guidelines of the Adult Treatment Panel III (ATP III) represent an updating of previous evidence-based recommendations, on the assessment of cholesterol effects, stressing the importance of the reduction of its plasma levels. The benefits resulting from the use of statins are not only related to lipid-lowering but also to its pleiotropic effects, such as anti-inflammatory action. Although, hepatotoxicity is a rare event (<2%), and often dose-related, in patients with liver disease fatal adverse effects have been reported using these molecules. The most important side effects consist of increased transaminase levels, abdominal pain, muscle weakness, increased levels of creatinekinase, up to rhabdomyolysis. The factors responsible for myopathy, during treatment with statins, may be related to the patient characteristics (age, female sex, alcoholism, hypothyroidism, systemic diseases, family history of myopathy, high consumption of grapefruit juice, large physical activity, major surgery, etc.) or to interaction with other medications (fibrates, cyclosporine, antifungals, macrolides, protease inhibitors, nefazodone, amiodarone, verapamil, etc.). Statins are inhibitors of HMG-CoA reductase undergoing first-pass hepatic metabolism. Except pravastatin, other molecules of this class are subject to hepatic metabolism in phase 1 mediated by CYP 450 isoenzymes. Therefore the indication for the use of HMG CoA reductase inhibitors must be evaluated by the physician on the basis of clinical necessity, and it is correct to start with low-dose drug administration, monitoring transaminases. Finally, it is appropriate to evaluate the drugs used simultaneously to statins that are metabolized at the level of the same cytochrome to reduce the risk of moderate and severe interactions. In fact the concomitant use of other drugs that are substrates of the same isoenzymes can determine the increase of statin concentration in the blood and consequently the risk of myopathy. The benefits associated with the use of statins in lowering cholesterol levels and preventing cardiovascular disease are superior to their potential risk of hepatotoxicity in patients with chronic liver disease. The use of statins in the course of liver disease is not absolutely contraindicated. However, their administration is not recommended in the course of acute hepatitis and daily abuse of alcohol. The starting dose of statins should be as low as possible, by monitoring transaminase levels, initially every two weeks, then every month. It is important not to underestimate the risk that the concomitant use of other drugs may lead to increased serum liver enzyme cytonecrosis and consequently to an increased risk of myopathy.

KEY WORDS: statins, liver disease, rhabdomyolysis, myopathy.

Background

Statins are drugs widely used worldwide as primary and secondary prevention of cardiovascular disease. Clinical guidelines of the Adult Treatment Panel III (ATP III) represent an updating of previous evidence-based recommendations on the assessment of cholesterol effects, stressing the importance of the reduction of its plasma levels. However, the appropriateness of treatment is based on judgment of physician and must always be correlated with the patient medical history (1). The benefits resulting from the use of statins are not only related to lipid-lowering but also to its pleiotropic effects, such as anti-inflammatory action (2). It must be considered that, since these drugs are administered in subjects at high risk of cardiovascular disease, their use is very often associated with other agents already taken by the patient, increasing the possible risk of interactions between different molecules. The most common adverse reactions during the use of statins such as rash, headache or disorders of

the gastrointestinal tract (3), are relatively mild and often transient. The most important side effects consist of increased transaminase levels, abdominal pain or muscle weakness, increased levels of creatinekinase, up to rhabdomyolysis (4). During treatment with statins, the factors responsible for myopathy may be related to the patient (age, female sex, alcoholism, hypothyroidism, systemic diseases, family history of myopathy, high consumption of grapefruit juice, large physical activity, major surgery, etc.) or to interaction with other medications (fibrates, cyclosporine, antifungals, macrolides, protease inhibitors, nefazodone, amiodarone, verapamil, etc.) (5). Recent studies suggest that even in liver disease, especially in those suffering from non-alcoholic steatohepatitis (NASH) there is indication to use statins because of the typical increased cardiovascular risk of these patients (6). Currently, there are no trials on the use of statins in chronic liver disease. However, a strict monitoring during their administration is recommended.

Statin metabolism and interaction with drugs

Statins are inhibitors of HMG-CoA reductase undergoing first-pass hepatic metabolism. Except pravastatin, other molecules of this class are subject to hepatic metabolism in phase 1 mediated by CYP 450 isoenzymes. Isoenzyme CYP3A4 is responsible for atorvastatin, lovastatin and simvastatin metabolism, while fluvastatin and rosuvastatin are metabolized mainly by CYP2C9 isoenzyme. The concomitant use of other drugs that are substrates of the same isoenzymes (fibrates, erythromycin, immunosuppressants, etc.) can determine the increase of statin concentration in the blood and consequently the risk of myopathy (Tab. 1). The direct relationship between plasma levels and toxicity of statins is not yet clear: it is possible that other variables can influence it such as genetic factors or concurrent administration of other lipid-lowering drugs (7). If it is not possible to predict which patients are at risk of rhabdomyolysis, close attention should be paid to those who are taking drugs metabolized by the same cytochrome. Finally, it should be stressed that in approximately 30% of patients administered with statin therapy in combination with drugs potentially able to interact, the side effects occur only in 3% of cases (8).

Statins in liver disease patients

The benefits associated with the use of statins in lowering cholesterol levels and preventing cardiovascular disease are superior to their potential risk of hepatotoxicity in patients with chronic liver disease. However, in the course of acute viral or alcoholic hepatitis, HMG-

Table 1 - Pharmacological interactions of statins.

STATINS	Pharmacological interactions (Drugs acting on Citocrome CYP-450)	
	Isoenzyme CYP-3A4	
Simvastatin/Atorvastatin/Lovastatin	Fibrates (Gemfibrozil)	Clarithromycin/Azithromycin/Erythromycin
	Warfarin	Digoxin
	Cyclosporine	Niacin
	Tacrolimus	Fusidic Acid
	Ketoconazole	Itraconazole
	Diltiazem	Amiodarone
	Lacidipine	Midazolam
	Nifedipine	Quinidine
	Verapamil	Sildenafil
	Nefazodone	Mibefradil
	Amprenavir	Indinavir
	Nelfinavir	Ritonavir
	Saquinavir	Sildenafil
	Antidepressant Tricyclics	Fluoxetine
	Sertraline	Tamoxifen
	Corticosteroids	Grapefruit juice
	Isoenzyme CYP-2C9	
Fluvastatin/Rosuvastatin	Fibrates (Gemfribozil)	Digoxin
	Warfarin	Mibefradil
	Diclofenac	Phenytoin
	Tolbutamide	Phenobarbital
	Not undergoing metabolism of CYP-450	
Pravastatin	Fibrates (Gemfibrozil)	Clarithromycin/Azithromycin/Erythromycin
	Digoxin	Niacin
	Warfarin	Cyclosporine

CoA reductase inhibitors should be avoided until liver function is restored (9). Although the major trials have excluded from the studies patients with a history or active liver disease, other studies documented that:

- hepatotoxicity, considered as a rare event (<2%), is often dose-dependent;
- increased levels of transaminases are often asymptomatic; jaundice or hyperbilirubinemia are rare conditions;
- the increase of transaminases levels usually occurs in the first 12 weeks of therapy, although the discontinuation of the drug restores normal transaminases values. With regard to the safety of these drugs in patients with liver disease, some suggestions were reported by the National Lipid Association (10).
- The increase of transaminases levels, about three times the normal value, is present in only 1% of patients. This percentage increases to 2-3% using atorvastatin at high doses (80 mg/day), especially if associated with ezetimibe. However, this relationship of cause and effect is not so straightforward in patients with NASH because in the course of it transaminase levels may fluctuate.
- Increased transaminases levels during treatment with statins are not necessarily indicative of damage or liver dysfunction, although these drugs increase the incidence of liver failure, the need for organ transplantation or death from liver-related causes. In literature there are rare cases of fatal rhabdomyolysis during the administration of statins (11). Since the association between liver failure and statins is rare, organ damage cannot be attributed directly to the use of such drugs. Finally, it is not possible to rule out that the possible reactions are idiosyncratic.
- Patients with liver disease usually do not have a particular cardiovascular risk having their blood cholesterol levels generally low. However, statins can be used in the course of NASH because this pathology is associated with an increased cardiovascular risk.

Recommendations

- If there is an indication for statin therapy in the course of non-active liver disease, these drugs shall be prescribed.
- It is recommended to start with low doses, making sure that the patient does not take alcohol.
- It is recommended to check serum levels of transaminases after the first two weeks of therapy.
- If transaminase levels are in the normal range or only mildly elevated, therapy can be continued by monitoring the enzyme values each month for three months and then four times a year.
- If it is needed to increase the dose, enzymes should be checked two weeks after dose-escalation, then monthly for three months after dose adjustment.
- If serum transaminase levels are doubled or tripled compared to normal, therapy should be discontinued waiting for the normalization of liver enzymes and reconsidering the use of another statin.

Conclusions

The use of statins in the course of liver disease is not absolutely contraindicated. However, their administration is not recommended in the course of acute hepatitis and daily abuse of alcohol. The starting dose of statin should be as low as possible, by monitoring transaminase levels, initially every two weeks, then every month. It is important not to underestimate the risk that the concomitant use of statins and other drugs may lead to increased serum liver enzyme cytonecrosis and consequently an increased risk of myopathy.

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