How Safe is the Hypolipidaemic Drug Treatment?

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The use of hypolipidaemic drugs and particularly of the 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors or statins for the treatment of dyslipidaemias, constituted one of the most important interventions in primary and secondary prevention of coronary artery disease (CAD). Statins[1-5], as well as the older hypolipidaemic drugs (nicotinic acid[6], cholestyramine[7] and fibrates[8]) have documented beneficial action on primary and secondary CAD prevention. The climate of "euphoria" that existed regarding statins' efficacy in treating hypercholesterolemia, their good tolerance by patients and the continuously appearing evidence on their beneficial action not only in CAD but also in other non-cardiac diseases has been disturbed by the recent withdrawal of cerivastatin by Bayer. Cerivastatin, which in Greece was distributed with Lipoban and Eltina preparations, is a synthetic statin and the most recent one among those approved [approval by the Food and Drug Administration (FDA) of the U.S. in 1997/ approval by the National Drug Organization in 1998]. Bayer voluntarily withdrew cerivastatin due to fatal cases of rhabdomyolysis that were observed. In the United States of America, 31 cases of fatal rhabdomyolysis were reported, most of which occurred in individuals on high doses of cerivastatin, in the elderly and those who received gemfibrozil (12 cases) concurrently. However, it should be noted that cerivastatin's tendency to induce rhabdomyolysis had been manifested relatively early. As shown in Table 1, 50% of rhabdomyolysis cases due to statins reported to the FDA within the period 1997-2000 were caused by cerivastatin.

The above side-effect brought to light the issue of hypolipidaemic drug safety. Since the majority of patients (>95%) receive statins (mainly) and fibrates, we will present data concerning the safety of these drugs, as they result from existing large studies.

Hypolipidaemic drugs and overall mortality

Hypolipidaemic studies concerning the use of the first hypolipidaemic drugs (nicotinic acid, cholestyramine, fibrates) in the last two decades have shown reduction of coronary events and of deaths due to CAD, both in primary as well as in secondary prevention of the disease. The question they left unanswered though was to what extent their administration leads to reduction of the overall mortality. Indicatively, we mention the Helsinki Heart Study[8], for the primary prevention of CAD with the administration of gemfibrozil for 5 years, which showed a 34% reduction of coronary events without any reduction of overall mortality. To the contrary, an unexpected increase of mortality was observed due to cerebral hemorrhage and accidents (15 in the treatment group vs. 5 in the control group [p=ns]). Thus, reasonable questions arose from this study on the targeted benefit of long-term administration of fibrates.

Statins that were introduced in clinical practice in 1987 [lovastatin (1987) was the first statin approved by the FDA, followed by simvastatin (1991), pravastatin (1991), fluvastatin (1993), atorvastatin

Table 1. Cases of statin-associated rhabdomyolysis reported to FDA (October 1997 - December 2000).

Statin	Number of rhabdomyolyses	% of the total	Without fibrates co-administration (%)
cerivastatin	387	50,1	48,3
simvastatin	187	24,3	87,7
atorvastatin	86	11,1	84,9
pravastatin	70	9,1	88,6
lovastatin	32	4,1	93,8
fluvastatin	10	1,3	80
total	772	100	67,9

(1996) and cerivastatin (1997)], brought an actual revolution in the area of hypolipidaemic drugs. There are three natural statins (lovastatin, pravastatin, simvastatin) that are products of fungal fermentation and three artificial statins (fluvastatin, atorvastatin and cerivastatin) that are more recent. The main mechanism of the action of statins is the inhibition of reductase of 3-hydroxy-3-methylglutaryl-co-enzyme A that constitutes the regulating enzyme for cholesterol synthesis. This leads to a reduction of intracellular cholesterol concentration and consequently to increased composition of LDL receptors (they are in the cellular membrane, particularly of hepatic cells) and facilitation of catabolism of circulating LDL molecules. As a result, LDL cholesterol is reduced by 25%-60%. Moreover, statins cause significant triglyceride reduction (20-40%), when triglycerides levels are > 250 mg/dl, as well as slight increase of HDL cholesterol (5-10%).

Statins are the only hypolipidaemic drugs that aside from their beneficial action in primary and secondary CAD prevention, have shown reduction of the total number of deaths, regardless of the causes. The documentation of this action was the result of well-designed studies where more than 15,000 individuals received pravastatin (WOSCOPS[1], CARE[3], LIPID[4]), simvastatin (4S)[2] and lovastatin (AFCAPS/TexCAPS)[5]. Furthermore, statins (pravastatin and simvastatin) reduce cerebral non-hemorrhagic episodes by 25-30% when administered to patients with established CAD[9,10].

In the 4S study, overall mortality was reduced by 29% (p=0.0003) in the simvastatin group vs. the control group, while in the LIPID study it was reduced by 22% (p=0.00002). Also, in the WOSCOPS primary CAD prevention study, overall mortality was reduced by 22%, reaching statistical significance (p=0.05). Thus, from the above studies was concluded that statins with a mean reduction of LDL cholesterol by approximately 30% led to reduction of overall mortality by 20-25%.

Hypolipidaemic drugs and carcinogenesis

Some of the first hypolipidaemic studies left the question of the eventual association of hypolipidaemic drugs with carcinogenesis unanswered. When data concerning gemfibrozil's safety were analyzed, following administration for 8.5 consecutive years (continuation of the Helsinki Heart Study), more deaths were recorded in the treatment group than in the control group (101 vs. 83, p=ns)[11] and this was attributed to higher mortality due to malignancy. In accordance with the most probable explanation, the side effects caused by gemfibrozil on the digestive system delayed timely diagnosis of certain malignancies. In the most recent VA-HIT study, where gemfibrozil was also administered to 1264 coronary patients for 5 years, no increased carcinogenesis was observed[12].

Detailed recording of all new malignant neoplasias was also effected in large hypolipidaemic studies with statins (WOSCOPS, CARE, LIPID, 4S, AFCAPS/TexCAPS). The results of the meta-analysis of these studies (Table 2) suggest that the percentage of fatal and non-fatal malignant neoplasias (with the exception of dermatological malignancies except melanomas) on the total of patients under treatment was no different than the one of the control group (6.5% vs. 6.6%). It is worth mentioning that in the CARE study, 12 cases of breast cancer were identified in the pravastatin group and only one in the control group, which was statistically significant (p= 0.002). This, however, was not verified either in the WOSCOPS study or in the LIPID study, where pravastatin was also administered. More

Table 2. Metaanalysis of WOSCOPS, AFCAPS/TexCAPS, 4S, CARE and LIPID regarding the side-effects of statins.

Study	Subgroups (number of individuals) depending on statin or placebo administration		Asymptomatic CK increase>10 times MNV	Transaminases increase>3 times MNV	Fatal or non fatal malignancies*	Violent deaths or suicides
WOSCOPS	pravastatin (40 mg)	3302	3	42	116	5
(primary CAD prevention)	placebo	3293	1	32	106	6
AFCAPS/TexCAPS	lovastatin (20-40 mg)	3304				
(primary CAD prevention)	placebo	3301	21	12	259	3
4S	simvastatin (20-40 mg)	2221	6	69	90	6
(secondary CAD prevention)	placebo	2223	1	56	96	7
CARE	pravastatin (40 mg)	2081	12**	66***	172	8
(secondary CAD prevention)	placebo	2078	7	73	161	4
LIPID	pravastatin (40 mg)	4512	8****	95*****	379	6
(secondary CAD prevention)	placebo	4502	10	85	399	11

CAD=coronary artery disease, MNV=Maximum normal values, CK=Creatinine kinase
* in malignancies, skin malignancies (except for melanomas) are not included
** it is not clear whether CK increase is asymptomatic or symptomatic nor if it is >10 times the MNV
*** total of individuals with SGOT increase only >3 times the MNV
**** total of individuals with symptomatic and asymptomatic CK increase
***** total of individuals with SGPT increase only >3 times the MNV

specifically, in the LIPID study with double the number of patients compared to the CARE study, only 10 cases of breast cancer were reported in the treatment group, the same as in the control group. Thus, the finding of the CARE study was characterized as incidental. On the contrary, in the AFCAPS/TexCAPS study, lower number of melanomas was observed in the lovastatin group compared to the control group (14 vs. 27, p= 0.04). Moreover, during the 8 year follow-up of individuals participating in the 4S study, who continued simvastatin for 3 additional years, lower number of malignancies was found in the treatment group compared to the control group[13]. Consequently, the chronic administration of natural statins, (up to at least 8 years for which we have data) does not seem to increase carcinogenesis[14] while on the contrary there are evidence suggesting a potential anti-neoplasia effect. Further *in vitro* studies have shown that statins may prevent the proliferation of neoplastic cells[15]. As a result of these observations, other studies are under way (phase I, phase II), that investigate the possible anti-carcinogenic effect of statins[16].

Hypolipidaemic drugs and violent deaths

In the Helsinki Heart Study[8] a relatively increased number of violent deaths and suicides had been observed in the gemfibrozil group. From the meta-analysis of the WOSCOPS, CARE, LIPID, 4S, AFCAPS/TexCAPS studies, 26 violent deaths or suicides were found in the treatment groups and 31 in the control groups (0.17 vs. 0.2%, p=ns), (Table 2). Also, in the VA-HIT study, where gemfibrozil was administered to ischemic patients, no difference was observed in violent deaths compared to the control group[12]. As a consequence, the administration of hypolipidaemic drugs is not associated with modification of the patients' behavior that could lead to violent deaths or suicides.

Hypolipidaemic drugs and hepatotoxicity

Hepatotoxicity is the side-effect that most often concerns the physician during the administration of statins. It is dose-dependent and it usually appears as an asymptomatic transaminase increase (0.5-2%). Rarely it may appear as hepatitis that is manifested as a flu (weakness, loss of weight, loss of appetite). If the transaminase increase is < 3 times the maximum normal values (MNV), the treatment is continued. If however the increase is >3 times the MNV, the treatment is interrupted and transaminase returns to normal within 2-3 months. Following the return of transaminase to normal, another statin may be used and this side-effect may not appear. From the meta-

analysis of the WOSCOPS, CARE, LIPID, 4S and AFCAPS/TexCaps studies on 15,420 individuals who received statin, asymptomatic transaminase increase >3 times higher than the MNV was observed in 1.9 % which was not different from the percentage of the control group that was 1.7% (p= ns), (Table 2). However in the AFCAPS/TexCaps study, when the overall percentage of individuals who presented SGPT increase above MNV was calculated, there was statistically significant difference in the lovastatin group vs. the control group (3.3 vs. 2.1%, p=0.003).

When statins are administered, transaminases control should be done before the beginning of treatment and should be repeated on 6 and 12 weeks and every six months throughout the patient's life. More specifically for pravastatin and fluovastatin, FDA suggest only one examination 12 weeks after the beginning of treatment or following dose increase of the statin and if the results are normal, there is no need to repeat them. Chronic active hepatitis is a contraindication for the administration of statins. We should also mention that a common cause of transaminase increase in patients under hypolipidaemic treatment is alcohol abuse. Also, obese dyslipidaemic patients might present liver infiltration that sometimes is accompanied by mild transaminase increase. Our practice when we assess mild transaminase increase (<3 times higher than the MNV) in patients receiving statins is to continue the treatment, to restrict the use of alcohol if this is the case and to repeat the examination of transaminase in 2 weeks. If an increasing trend is seen in the transaminase levels we interrupt the statin administration until transaminase returns to normal, and then we re-administer another statin, preferably hydrophilic (e.g. pravastatin) at low doses.

Finally, transaminases values may be increased due to administration of fibrates. It is however more rare and this is why regular transaminase control is not suggested in case of fibrates administration. In case of concurrent administration of statins with fibrates, there is increased risk for asymptomatic transaminemia. In a recent meta-analysis this was observed in 3.2 %[17].

Hypolipidaemic drugs and myopathy

It constitutes a rare (<1%) and dose-dependent side-effect of statins. It may manifest as myalgia (muscle pain or muscle weakness or both, with normal creatinine kinase levels [CK]), myositis ("myalgia" with increased CK) and less often as rhabdomyolysis where muscle symptoms are accompanied by high CK increase (more than 10 times of MNV). In the WOSCOPS, CARE, LIPID, 4S and AFCAPS/TexCAPS studies, asymptomatic CK increase > 10 times the MNV was observed in 0.32% of the treatment groups and 0.26% in the control groups (p=ns), (Table 2). However, there are no analytical data on all the myopathy manifestations in the these studies. Also, 2 cases of non-fatal rhabdomyolysis were observed in the treatment groups, the same as in the control groups.

Rhabdomyolysis is characterized by muscle pain, weakness, fever, dark brown urine and very high CK increase (usually >10.000 U/L). If not diagnosed early and if the drug administration continues, it might lead to acute renal failure and death. The best preventive measure is to suggest to the patient to immediately stop taking the drug in case unexplained muscle pain appears and to contact a physician. Although CK increase does not necessarily mean myopathy development, it is preferable to determine CK before statin administration, because asymptomatic CK increase is common and it is useful to know the baseline value in order to perform comparative assessment in the future[18].

The myopathy risk is higher when the statins are administered with fibrates (particularly gemfibrozil) or nicotinic acid (combination of nicotinic acid with statin is considered less myotoxic than the combination of statin with fibrate), in hepatic or renal failure, hypothyroidism, advanced age, administration of certain drugs or agents that inhibit P-4503A4 cytochrome (Table 3). Four out of the 6 existing statins are metabolized in P-4503A4 cytochrome (Table 4)[19].

The Drugs Side-Effects Data Bank of the World Health Organization (INTDIS) notes that myopathy (myalgia, myositis, rhabdomyolysis) have been observed during the administration of all statins (class effect)[20]. *In vitro* studies showed that pravastatin compared to lovastatin and simvastatin is less myo-

Table 3. Clinically significant inhibitors of cytochrome P-450 3A4.

1) Erythromycin, clarithromycin, azithromycin
2) Cyclosporin
3) Antifungal: fluoconazole, ketoconazole, itraconazole
4) Verapamil
5) Anti-viral drugs: ritonavir, nelfinavir
6) Grapefruit juice (on consumption >1 liter daily)

Table 4. Pharmacokinetics of statins.

Statin	Half life (hrs)	Binding to plasma proteins (%)	Effect of food on absorption	Metabolism through cytochrome P-4503A4	Entry to the CNS	Renal clearance (%)
lovastatin	2	95	increase of absorption	yes	yes	10
pravastatin	1-2	50	reduction of absorption	no*	no	20
simvastatin	1-2	95	no	yes	yes	13
fluvastatin	1,2	98	no	no**	no	<6
atorvastatin	14	98	no	yes	no	2
cerivastatin	2-3	99	no	yes	yes	33

CNS=central nervous system
* metabolism through other paths
** metabolism through cytochrome P-4502C9

toxic, possibly due to the lower absorption by muscle cells[21]. The exact mechanism of myotoxicity by statins is not known.

The sensitivity of an individual to statin administration depends on the status of cytochrome P-4503A4. There is large variation in the expression of isozymes of cytochrome P-450 among individuals. There are those with low activity levels of P-4503A4 cytochrome. As a result, those individuals present higher probabilities of myopathy due to statin use, when they receive at the same time cytochrome P-4503A4 inhibitors[22]. In such cases, the administration of pravastatin and fluovastatin that are not metabolized through cytochrome P-4503A4 does not seem to increase the myotoxicity risk[23].

In international literature[17, 24, 25] 31 cases of rhabdomyolysis have been described due to co-administration of statin (21 on lovastatin, 5 on simvastatin, 4 on cerivastatin and 1 on atorvastatin) and fibrates (gemfibrozil in all cases). In the vast majority (93%) symptoms appeared within the first 12 weeks from the beginning of treatment. Mean CK was 48.300 (1.900-357.900 U/L). 66% developed acute renal failure and 6 of the patients required hemodialysis. One of these cases was fatal - a man, 68 years old, with renal failure (diabetic nephropathy) who received combination of simvastatin (80mg/day) and gemfibrozil (600 mg b.i.d.)[25]. It should be noted that the presence of gemfibrozil in all the described cases of rhabdomyolysis is explained to a certain extent by its wider use compared to other fibrates. Also worth mentioning is the fact that bezafibrate and ciprofibrate are not marketed in the US. In the Drugs Side-Effects Data Base of the World Health Organization, there are reports of rhabdomyolysis in the case of co-administration of statins with bezafibrate and phenofibrate. The mechanism through which rhabdomyolysis is caused in case of co-administration of statin and fibrate had not been identified yet. Initially, it was attributed to interactions on cytochrome P-4503A4. However, it seems more likely that it is due to direct toxic action of both drugs on the skeletal muscles.

There are no comparative studies to assess the degree of safety of each statin when co-administered with fibrate. The largest volume of information on the safety of this combination regards natural statins which are marketed for a longer period of time. In the case of cerivastatin, some time before its withdrawal, Bayer had proceeded to the modification of the product's characteristics due to cases of rhabdomyolysis that occurred when the drug was combined with gemfibrozil. Thus, the pre-existing warning to avoid co-administration of cerivastatin and gemfibrozil was modified to total contraindication. All this occurred before publication of data on the increased incidence of rhabdomyolysis. Consequently, we think that the best criterion to evaluate the safety of a hypolipidaemic drug is the existence of data from long-term controlled clinical studies.

The incidence of myopathy due to administration of statins with fibrates reaches 1% according to

Shepherd[26]. A recent meta-analysis of 36 studies[17] with overall 1,674 patients who received combination of statin and fibrates showed myopathy rates of 0.12%. This percentage, however, changed to 2% when myalgias were also included. This meta-analysis may under-estimate the risk of myotoxicity since in most of these studies, patients with renal failure or hypothyroidism were excluded, which are conditions that increase the myotoxicity risk.

In a recent large retrospective study in the United Kingdom[27], where they studied the risk of myopathy in 17.219 dyslipidaemic patients and compared it to the risk in 50.000 individuals from the general population, it was found that the myopathy risk is extremely low. In particular, myopathy was observed in 2.3/10.000 individuals/year among those who were on hypolipidaemic therapy and in 0.2/10.000 individuals/year in the general population. However, as regards the relative risk, individuals on statin had 7 times higher probability to develope myopathy, while individuals who received fibrate had 42 times higher risk of myopathy compared to the general population. The myotoxicity risk in fibrate administration is increased in case of renal failure.

In an effort to combine the above, we would say that the myotoxicity risk in case of statin or fibrate administration is rare but present. Even more rare is the rhabdomyolysis risk. The risk of myotoxicity becomes higher when there is co-administration of statins with fibrates. This combination must be done very carefully and only if the physician in charge deems that the benefit is higher than the side-effects risk. Our own practice in case of co-administration of statins with fibrates is to administer low doses of statins and fibrates and to proceed to transaminase and CK measurement at 6 and 12 weeks after the beginning of treatment and then every three months. Prior to treatment initiation, transaminase and CK are always examined. In addition, we do not proceed to co-administration immediately but we initially administer one of the drugs and add the second one approximately two months later. The fibrate is administered in the morning and we prefer combining it with hydrophilic statin with short half-life (e.g. pravastatin). We also instruct patients to interrupt the hypolipidaemic drugs in case of unexplained muscle pain and to come for CK and TSH control, since hypothyroidism predisposes to myopathy. If we believe that myalgias are due to the treatment, even if CK is not increased, we prefer not to re-administer the same treatment. If in an occasional laboratory control of a patient on statin we observe asymtpomatic CK increase that did not pre-exist and is not explained by previous muscular strain, we interrupt the hypolipidaemic treatment if CK is $\geq$3 times higher than MNV. The suggestions by the American Cardiology Society are much more flexible since the threshold for the interruption of statins is at higher CK levels (CK >10 times higher than MNV)[18]. If CK is increased but <3 times than the MNV and the patient is asymptomatic, we ask for a CK re-assessment in 2 weeks. If we consider that there is an increasing trend in CK levels, we discontinue treatment. When the patient on statin must receive macrolides due to infection, it is preferable to interrupt the statin for the time period of macrolides administration. When dyslipidaemic patients receive verapamil chronically, we prefer administration of statins that are not metabolized through P-4503A4 cytochrome (pravastatin, fluovastatin). Finally, when statin is co-administered with cyclosporine (common combination in heart transplant patients), data show that the safest combination is with pravastatin[28].

Other side-effects

Statins may also present other side-effects such as gastrointestinal disorders (indigestion, nausea, constipation), skin rash, peripheral neuropathy and manifestations from the central nervous system such as insomnia, nightmares. In this last case, we prefer statins that do not cross the blood brain barrier such as pravastatin, fluovastatin, atorvastatin.

Finally, fibrates may cause gastrointestinal disorders, increase of bile lithogenesis and skin rash.

Conclusion

Statins exerts a clear beneficial action in primary and secondary CAD prevention. They also prevent strokes in CAD patients and they might have a beneficial effect on non-cardiac diseases[29] such as neoplasia[15,16], osteoporosis[30] and senile dementia[31]. They are well-tolerated drugs with very few side-effects. More specifically, natural statins (lovastatin, pravastatin and simvastatin) for which there are survival studies as well as long-term (up to eight years) systematic follow-up of patients, are considered extremely safe drugs. Patients on statin must undergo regular transaminase control and must interrupt the treatment when transaminase values exceed three times the MNV. Also, treatment should be discontinued in

case of unexplained muscle pain. The appearance of side-effects must not deprive the dyslipidaemic patient of the benefit of their use. Thus, when a statin is interrupted due to side-effects another statin should be administered with caution, since side-effects are not necessarily the same.

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