

Safety of statins when response is carefully monitored: a study of 336 heart recipients

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Abstract

Background. Statins are used as first-line drugs against hypercholesterolemia after heart transplantation. Randomized clinical trials have shown that they reduce cholesterol levels, and the incidence of rejection and coronary vasculopathy. Adverse effects have been related to the use of certain statins, high statin dosages, comorbidities, and coadministration with cyclosporine. However, estimation of the risk of adverse effects for a given patient is difficult. The aims of this study were to determine the incidence of various kinds of adverse effect of statins; to evaluate certain potential risk factors; and to assess the efficacy of early response to signs of adverse effects.

Methods. Between April 1991 and December 2003, we retrospectively evaluated 336 heart transplant patients (including 55 women) with regard to the occurrence of possible adverse effects of statins (rhabdomyolysis, myalgia, hepatotoxicity, high CK without muscle symptoms, and others). Resolution on reduction of dosage or discontinuance and/or change of statin were deemed to constitute confirmation of cause. Relations were sought between adverse effects and age, sex, immunosuppressive therapy, kidney failure, body mass index (BMI), arterial hypertension, and diabetes mellitus.

Results. Possible adverse events of statins were suffered by 60 patients, all of them men. The causal role of statins was confirmed in 41 (12.2% of all 336): hepatotoxicity was suffered by 13, high CK without muscle ache or weakness by 18, rhabdomyolysis by 5, myalgia by 3, and other effects by 2. The incidence of confirmed statin-related complications was higher among patients with BMI >29 kg/m² than among those with lower BMI ($P = .055$). None of the patients with confirmed statin-related complications needed dialysis, none died, and permanent suspension of statin treatment was only necessary in 13 cases (3.9% of the 336).

Conclusions. Some 10% to 20% of HT patients appear to suffer adverse side effects of initial statin therapy. However, early detection of such effects through diligent clinical and analytical monitoring allows the therapy to be modified in time to minimize the appearance of severe complications. In only a minority of cases permanent suspension of statin therapy is necessary.

Hypercholesterolemia is common after heart transplantation (HT); 60% to 80% of HT patients showing increased dyslipidemia after transplant.¹ High cholesterol levels have been associated with rejection, the development of coronary vasculopathy, impaired endothelial function, myocardial infarct, and death.² Randomized clinical trials^{3, 4, 5, 6, 7, 8 and 9} have shown that the use of statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase) reduce blood cholesterol levels and coronary disease following HT. In our institution, statins are considered to be an important component of early posttransplant therapy. Lipid-lowering treatment may occasionally lead to adverse effects, especially when it involves certain statins or high doses, or when it coincides with cyclosporine therapy.¹⁰ It is desirable to be able to estimate the risk of such effects for an individual patient from consideration of risk factors. The aims of this study of 336 statin-treated HT patients were to determine the incidence of various kinds of adverse effect of statins; to evaluate certain potential risk factors; and to assess the efficacy of early response to signs of adverse effects.

Methods

Between April 1991 and December 2003, 444 patients received heart transplants in our institution. We retrospectively evaluated the 336 who were older than 16 years at HT and who after HT had survived for more than 1 month and received lipid-lowering therapy with statins. In all cases, adverse effects of statin treatment was monitored by routine laboratory determinations of creatine kinase (CK), alanine transferase (ALT), and aspartate transferase (AST) every 3 months, or every 4 weeks if the statin dose had been increased, and by periodic clinical examination. The following conditions were noted as possible adverse

effects of statins: rhabdomyolysis (CK >1000 U/L); high CK (CK <1000 U/L but greater than three times previous level, without muscle symptoms); hepatotoxicity (AST or ALT levels greater than three times the previous level or twice the upper limit of the normal range); myalgia (muscle ache without CK elevation); and others (increase in LDH or bilirubin levels). The therapeutic response to the appearance of these conditions was to reduce the statin dosage; to suspend statin treatment for as long as was required to resolve the symptoms; or to change the statin, either immediately or after temporary suspension of treatment. They were attributed to the use of statins if they resolved when so treated. Other data noted for each patient were age, gender, immunosuppressive therapy, body mass index (BMI), and whether the patient had arterial hypertension, kidney failure, or diabetes mellitus.

Results

Of 336 patients (mean age 53 years), 55 were women (16.4%). Statin therapy was initiated with pravastatin in 269 cases (80.1%), simvastatin in 65 (19.3%), and atorvastatin in 2 (0.6%). Thirty-one patients (9.2%) had diabetes mellitus before HT, and 65 (19.3%) had a BMI >29 kg/m². More than 50% (172 patients) had arterial hypertension after HT.

Possible adverse effects of statins were observed in 60 of the 336 statin-treated patients (17.9%), all of them men: hepatotoxicity in 26 (7.7% of the 336), high CK without muscle ache or weakness in 20 (6.0%), rhabdomyolysis in 6 (1.8%), myalgia in 4 (1.2%), and other effects in 4 (1.2%). In 3 of these 60 cases (5%), the statin dosage was reduced but not suspended; in 11 (18.3%) treatment was suspended temporarily and resumed with the same drug; in 18 (30%) treatment was suspended temporarily and later resumed with another statin; in 6 (10%) the statin was changed without prior suspension of treatment; and in 22 (36.7%) statin treatment was suspended indefinitely.

In 41 of the 60 cases in which possible adverse effects of statins were observed, resolution of these effects led to their being attributed to statin treatment. In 13 of these 41 cases (3.87% of the 336 statin-treated patients), the effect was hepatotoxicity, in 18 (5.36%) high CK without muscle ache or weakness, in 5 (1.49%) rhabdomyolysis, in 3 (0.89%) myalgia, and in 2 (0.59%) other effects.

Among the 336 statin-treated patients, the incidence of confirmed adverse effects was greater when BMI >29 kg/m², but the difference was not statistically significant ($P = .055$). Of the 41 patients with confirmed adverse effects, 19 were receiving cyclosporine, prednisone, and mycophenolate mofetil immunosuppressive therapy (46.3%); 11 were taking cyclosporine, prednisone, and azathioprine (26.8%); and 6 were taking tacrolimus, prednisone, and mycophenolate mofetil (14.6%). The occurrence of adverse effects was not correlated with immunosuppressive therapy, diabetes mellitus, age, arterial hypertension, or renal dysfunction.

In 20 of the 41 patients with confirmed adverse effects of statin, the statin apparently responsible was pravastatin (7.43% of pravastatin-treated patients), but in our study, as in other studies¹¹ this drug was in no case associated with severe adverse effects. Simvastatin was apparently responsible for seven cases of adverse effects (10.76% of simvastatin-treated patients), including four of the five cases of rhabdomyolysis. The other one that developed rhabdomyolysis was initially put on atorvastatin. However, none of the 41 patients with confirmed adverse effects of statins needed dialysis, and none died. In 3 of these 41 cases, resolution of symptoms followed dose reduction, in 3, an immediate change of statin, in 8, temporary suspension followed by resumption with the same statin, and in 14, temporary suspension followed by resumption with a different statin; in 13 cases, statin treatment was not resumed.

Discussion

Aggressive statin therapy after heart transplantation has in several trials been found to reduce cholesterol levels, the incidence of major rejection, the incidence of coronary vasculopathy, and mortality. Therefore, treatment with statins is recommended for all HT patients in the absence of contraindications. However, statin treatment has its risks, including the possibility of fatal rhabdomyolysis. Although the estimated incidence of fatal rhabdomyolysis per 1 million prescriptions among patients of all kinds is zero for fluvastatin and only 0.04 for pravastatin, 0.12 for simvastatin, and 0.19 for lovastatin,¹² the corresponding incidences among HT patients are probably higher, because the risk factors for complications of statin therapy include treatment with drugs commonly employed in post-HT therapy, such as cyclosporine. Other reported risk factors include advanced age, small or frail constitution, chronic kidney failure, abuse of ethanol, recent surgical operation, and high consumption of grapefruit juice.^{13 and 14} Ideally, the risk of complications of individual patients should be estimated, and the type and dosage of statin chosen accordingly.

Some of the complications of statin therapy, notably liver damage, can also be caused by other drugs taken by HT patients. If these complications arise in HT patients, they cannot automatically be assumed to be secondary to statin treatment. In this study, complications were therefore deemed a result of statin treatment only if they resolved on reduction of dosage, suspension of treatment, or change of statin.

In this study it was not the general rule for patients to suffer adverse effects of statins, but the incidence was not so low as in some other studies,^{6, 7, 8, 9 and 14} even when we considered only cases in which the attribution to statin treatment was confirmed by remission. This was probably because the CK and transaminase thresholds used to define adverse effects were lower than those used in other studies. By contrast, in this study the incidence of severe adverse effects (death or kidney dysfunction requiring dialysis) was zero, which suggests that early diagnosis and an appropriate response can avoid advanced complications.

Although all adverse effects concerned men, this finding should be viewed with caution because there were only 55 women in the study group (16.4%). Although the difference in incidence of adverse effects between patients with BMI >29 kg/m² and those with BMI <29 kg/m² lacked a few tenths of a percentage point to be regarded as statistically significant, the higher incidence among those with greater BMI should probably be kept in mind in evaluating individual patients.

In conclusion, statins should be considered as first-line drugs against hypercholesterolaemia and its consequences following heart transplantation. The low incidence of severe complications in this study confirms that these drugs are safe if the patient's response is monitored by clinical examinations and laboratory tests, if appropriate marker thresholds are used to warn of the onset of adverse effects, and if appropriate action is taken in response to positive results of these tests or examinations.

References

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