Efficacy and safety of statins in the treatment of diabetic dyslipidemia

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RÉSUMÉ

Prérequis : L'ATPIII (Adult Treatment Panel III) recommande les inhibiteurs de l'hydroxy-3-methylglutaryl coenzyme A réductase ou les statines en première intention pour le traitement de la dyslipidémie du diabétique. Ces dernières sont caractérisées par leur efficacité et leur bonne tolérance. Ainsi, plusieurs essais cliniques ont démontré que les statines réduisent le risque d'événements cardiovasculaires.

But: L'objectif de notre étude est d'évaluer l'efficacité et la tolérance des statines chez les diabétiques de type 2.

Méthodes : Cette étude a concerné 120 diabétiques de type 2 présentant une hyperLDL-émie, la moyenne du LDL-Cholestérol au début de l'étude était 4,26±0,82 mmol/l, la moyenne du cholestérol total était 6,52±0,75mmol/l, la moyenne du HDL-cholestérol était 1,15±0,31 mmol/l et la moyenne des triglycérides était 1,77±0,67mmol/l. Tous ces patients ont été soumis à un traitement par statines.

Résultats : Les résultats montrent qu'il y a une réduction significative du cholestérol total (P=2.10-3) et du LDL-cholestérol (P = 5.10-4) avec les statines ; la moyenne du LDL-cholestérol est réduite de 4,26±0,82 mmol/l au début de l'étude à 2,8±0,59 mmol/l après 12 mois de traitement. Le pourcentage de réduction du LDL-cholestérol est de 24 à 35% ; en outre, le pourcentage de réduction du cholestérol total est de 22 à 28%, la réduction moyenne des TG était entre 11 et 16%. Quant au HDL-Cholestérol, Il y a une augmentation mais non significative. Parmi ces 120 patients, 5.1% ont présenté une élévation modérée de la créatine kinase (CK) et 2% une élévation des transaminases. Les myalgies sont rapportées approximativement dans 3.6% des cas.

Conclusion: Ces résultats soulignent l'efficacité des statines dans la correction des anomalies lipidiques chez le diabétique de type 2, en l'occurrence l'hyper-LDLémie ; considéré comme un facteur de risque cardiovasculaire majeur. Ainsi, Les statines sont caractérisées par leur excellente tolérance.

Mots-clés

Statines - LDL-Cholestérol - Cholestérol total - Triglycéride - Créatine kinase - Transaminases.

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SUMMARY

Background: The Adult Treatment Panel III recommends 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins as first-line-lipid-altering therapy for all adult patients with diabetes mellitus. This is based on the well-characterized efficacy and safety profiles of this class of agents as well as several clinical trials demonstrating that statin treatment reduces the risk of cardiovascular events.

Aim : The objective of our study was to investigate the efficacy and safety of statin therapy in patients with diabetes type 2.

Methods: We analyzed data from 120 individuals with diabetes type 2. For all patients, the mean baseline LDL-cholesterol level was 4,26±0,82 mmol per liter, the total cholesterol level was 6,52±0,75 mmol/l, HDL-cholesterol level was 1,15±0,31 mmol/l and triglyceride level was 1,77±0,67 mmol/l.

Results: There was a significant reduction in total cholesterol (P = 2.10-3) and LDL-cholesterol (P = 5.10-4) with statins; the mean LDL-cholesterol level was reduced from 4,26±0,82 mmol/l at baseline to 2,8±0,59 mmol/l at 12 months. The percentage variation of LDL-cholesterol was between 24 and 35%; in addition, the percentage reduction of total cholesterol was between 22 and 28%, the mean reduction in TG levels was between 11 and 16%.There was a no significant increasing in HDL cholesterol. Among these 120 patients, 5,1% had a moderate CK elevation. Moreover 2% had a significant elevation of transaminase levels. Statins have also been associated with muscle-related adverse events; so milder complaints (myalgia) are reported by approximately 3,6% of patients who take statins.

Conclusion: Statins as highly efficacious agents for the lowering of low-density lipoprotein-cholesterol (LDL-C) revolutionized treatment of hypercholesterolemia, a long established risk factor for premature coronary heart disease and they are not only exhibit a remarkely high benefit to risk ration, but are equally characterized by a safety profile with excellent tolerance.

Key-words

Statins - LDL-Cholestero - Total cholesterol - Triglycerides - Creatine kinase - Transaminases.

Cardiovascular diseases (CVD) remain a primary cause of morbidity and mortality among patients with type 2 diabetes despite the availability of effective therapies to treat major risk factors such as elevated blood pressure and cholesterol levels. Current evidence-based treatment guidelines for cholesterol management focus on prescription of hydroxymethylglutaryl-CoA reductase inhibitors (statins) to reduce LDL cholesterol levels. In addition, statins can reduce triglycerides and increase HDL-cholesterol.

This study aimed to investigate the efficacy of statins on lipid abnormalities in type 2 diabetes and to assess their tolerance.

PATIENTS AND METHODS

We analyzed data from 120 individuals with diabetes type 2. The records of patients being medically treated for dyslipidemia employing statins to achieve an LDL-Cholesterol < 100 mg/dl. We measured total cholesterol (TC), triglyceride (TG) and high-density lipoprotein (HDL) by enzymatic methods. LDL was calculated from these. In addition, patients had a transaminase measurement and creatine kinase (CK) testing at the baseline and at 3, 6 and 12 months.
Statin treatment was prescripted at the time when we discover high LDL-cholesterol. The data base query asked for the prescription of any of the following agents: simvastatin, atorvastatin, pravastatine or fluvastatin. All patients who were taking statins and for whom test results showed significantly or moderately elevated serum levels of tansaminases or CK were identified. Significant elevations were defined as more than 3 times the upper limit of the normal range for tansaminases (alanine aminotransferase : ALAT or aspartate aminotansferase: ASAT) and more than 5 times the upper limit of the normal range for CK. An abnormal test result was considered attributable to statin use if it could be reasonably explained by no other medical condition or medication use, or if it resolved when the medication was discontinued.

STATISTICAL ANALYSIS
All the data were entered into Epi Info program for statistical analysis. Results are presented as the mean value ± SD for continuous variables and as the percentage of total patients of categorical variables. The independent samples t-test and chi-square test were used for comparison of continuous and categorical variables, respectively.

RESULTS

The characteristics of patients are shown in table 1. The distribution of statin use among the patients was 58,5% simvastatin (10-20mg/day), 33,4% atorvastatin (10-20 mg/day), 4,5% pravastatin (20 mg/day) and 3,6% fluvastatin (40 mg/day).

Table 1 : patient's characteristics

characteristics	Diabetic subjects
Age (years)	54,3±9,1
Sex	F: 48,6%
	H: 51,4%
Body mass index (Kg/m2)	29,4±3,7
Duration of diabetes (years)	11,7±8,3
Hemoglobin A1C (%)	7,1±1,4

Table 2 summarizes laboratory values at baseline and follow-up and change in values from baseline. For all 120 patients, the mean baseline LDL-cholesterol level was 4,26 ± 0,82 mmol/l (1,65±0,32 g/l), the total cholesterol level was 6,52±0,75 mmol/l, HDL-cholesterol level was 1,15±0,31 mmol/l and triglyceride level was 1,77±0,67 mmol/l. It is shown in table 2, there was a significant reduction in total cholesterol and LDL-cholesterolwith statin, the mean LDL-cholesterol level was reduced from 4,26 ± 0,82 mmol/l (1,65±0,32 g/l) at baseline to 2,8±0,59 mmol/l (1,1±0,23 g/l) at 12 months(P = 5.10-4) .
The percentage variation of lipids are shown in table3.Mean

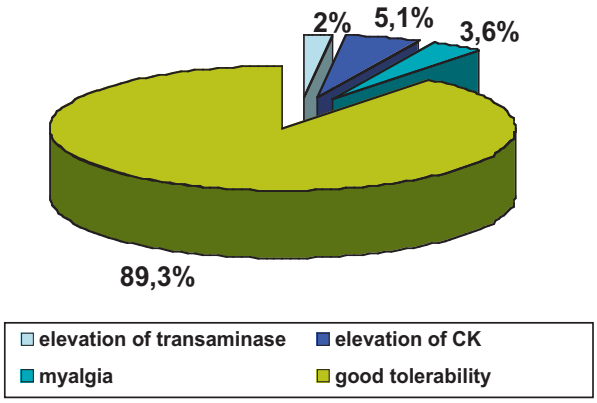
Table 2 : Laboratory values at baseline and follow-up and change in values from baseline-

characteristics	baseline	3 months follow up	6 months follow up	12 months follow up
Total cholesterol (mmol/l)	6,52±0,75	5,05±1,03 (P = 4.10^{-3})	4,86±0,84 (P 3.10-3)	4,7±0,64 (P 2.10-3)
LDL cholesterol (mmo/l)	4,26±0,82	3,04±1,03 (P = 10^{-3})	2,7±1,1 (P = 10^{-4})	2,8±0,59 (P = 5.10^{-4})
HDL cholesterol (mmol/l)	1,15±0,31	1,24±0,3 (P = NS)	1,3±0,31 (P = NS)	1,18±0,48 (P = NS)
Triglycerides (mmol/l)	1,77±0,67	1,58±0,73 (P = NS)	1,46±0,63 (P = 0,005)	1,51±0,73 (P = 0,03)

reduction in LDL-cholesterol was between 24 and 35%; in addition, the percentage reduction of total cholesterol was between 22 and 28%, and the mean reduction of TG levels was between 11 and 16%.There was no significant increasing in HDL cholesterol.

Among these 120 patients, 4,1% had a moderate CK elevation and 1% who had a significant abnormal CK value. Moreover 2% had a significant elevation of transaminase levels. Statins have also been associated with muscle-related adverse events. Milder complaints (myalgia) are reported by approximately 3,6% of patients who beneficed of statin's treatment.(figure 1).

Figure 1 : Severity of liver cirrhosis attested by the Child Pugh score paralleled impairment in nutritional status



DISCUSSION

The efficacy of statin therapy on LDL lowering and reduction of cardiovascular events is well established (5-9). In the present study, statin therapy decreased LDL-cholesterol, total cholesterol and triglyceride. Additional evidence for the efficacy of statins in diabetic dyslipidemia comes from more recent, larger clinical trials. The Scandinavian Simvastatin Survival Study (4S) ushered in the era of megatrials on hypolipidaemic therapy (21). A total of 4444 patients with angina or prior myocardial infraction and serum cholesterol 212-309 mg/dl were put on either Simvastatin (dose range 10-40 mg/day) or placebo and followed up for a median of 5,4 years. Total cholesterol was reduced by 25% and LDL-cholesterol by 35% in the treatment group. The next major study was the West of Scotland Coronary Prevention Study (WOSCOPS) (20). A total of 6595 men were treated on either pravastatin 40 mg/day or placebo, and followed up over an average of 4,9 years. Total cholesterol was reduced by 20% and LDL cholesterol reduced by 26% with treatment. The following year saw the publication of the cholesterol and Recurrent Events (CARE) study (18). This studied patients with a past history of a myocardial infraction, but who had average cholesterol levels of 209±17 mg/dl. A total of 4159 patients had a median follow-up for 5 years. Total cholesterol reduced by 20% and LDL cholesterol by 28%. The Long Term Intervention with Pravastatin in Ischemic Disease (LIPID) study emphasized the importance of hypolipidaemic therapy in the secondary prevention setting (16). A total of 9014 patients were enrolled in this placebo-controlled study and followed-up over a mean of 6,1 years. Pravastatin 40 mg daily reduced total cholesterol by 25% compared to placebo.

The focus returned to primary prevention, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) (17), the effects of lovastation 20-40 mg/day on average risk healthy population with normal total cholesterol levels of 221±21 mg/dl but having low HDL-cholesterol < 45 mg/dl for men and < 47 mg/dl for women. After one year, lovastatin treatment significantly reduced total cholesterol levels by 18%, LDL cholesterol by 25% and increased HDL-cholesterol by 6%.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study (11) looked at the effect of atorvastatin used early in the acute coronary syndromes (ACS); atorvastatin treatment reduced total cholesterol by 34% and LDL-Ch by 52%.

The Atorvastatin Diabetes Study (CARDS) recruited 2838 diabetic patients and randomized them to atorvastatin 10 mg/day or placebo (4). Treatment with atorvastatin reduced total cholesterol by 26% and LDL-cholesterol by 40%.

In the publication of the Heart Protection Study (HPS), patients recruited were defined as being at high risk of coronary disease, presence of non coronary atheromatous disease or diabetes (7). A total of 20536 patients were randomized to receive simvastatin 40 mg/day or placebo. After 5 years, simvastatin reduced total cholesterol by a mean of 1,2 mmol/l (20,3%) and LDL-cholesterol by 1,0 mmol/l (29,4%).

The mechanism of action of statins is the increasing LDL-receptor-mediated clearance of apoB lipoproteins, particularly LDL, when baseline LDL receptor activity is reduced.however,

Table 3 : Laboratory values at baseline and follow-up and change in values from baseline-

Change from baseline	3 months follow up	6 months follow up	12 months follow up
Total cholesterol	-22,4%	-24%	-28%
LDL cholesterol	-24%	-33%	-35%
HDL cholesterol	+5%	+12%	+10%
Triglycerides	-11%	-16%	-15%

in patients with dyslipidemia associated with insulin resistance/T2DM, where secretion of VLDL and LDL into the circulation is prominent, statins can improve lipid levels by reducing the assembly and secretion of apoB lipoproteins by inhibiting cholesterol synthesis (15, 19, 22). However, there is evidence that statins reduce VLDL-TG secretion, the molecular basis for statin-mediated reductions in VLDL-TG secretion are unknown, although some investigators have suggested that statins may stimulate hepatic expression of the gene for peroxisome proliferator-activated receptor and its target gen (8,10). Regardless of the mechanisms, the ability of statins to lower both LDL and VLDL levels in patients with T2DM makes them useful agents for treating the dyslipidemic state, which is characterized by overproduction of all apo B lipoproteins. In our study, statins decreased triglyceride, in addition to decreasing low density lipoprotein-cholesterol. The mean TG level was reduced 1,77±0,67 mmol per liter at baseline to 1,51±0,73 mmol/l per liter at 12 months.

Among the 120 patients for whom serum transaminase level was tested, 2% were identified as having an abnormal value and 5,1% of the patients had a moderate elevation of CK (501-1000 u/l). The reported rates of serious adverse events (SAEs) among statins as a class have been very low (<1%) and include a slight risk for elevation of liver enzymes and myopathy (12).

The rate of elevated liver transaminase levels reported in product information literature ranged from 0,2% to 2,3%, increasing in a curvilinear relation to the statin dose(13,14). Elevated CK levels are biochemical markers of the muscle damage associated with myopathy from any cause. In the clinical setting, asymptomatic elevations of CK level of less than 5 times upper limit of normal be considered benign, whereas elevations of 5 to 10 times upper limit of normal require evaluation. Myopathy has traditionally been defined as CK level greater than 10 times upper limit of normal with symptoms. In the study of Christopher (6), of 1014 patients who had a statin on their medication, 1% had a significant elevation and 0,5% a moderate elevation of transaminase levels. Moreover, 0,9% patients had at least one significantly abnormal CK elevation and 2,1% of patients who had a moderate CK elevation.

This present study suggests that among patients receiving statin medications in a primary care practice, the risk of severe transaminase or CK abnormalities attributable to statins is low. Statin-associated myalgia affected approximately 3,6% of patients in our study. The incidence of myalgia, which is not as well defined as that of more serious myotoxicities, is reported in randomized controlled trials (RCTs) as ranging from 1,5% to 3% (1,2). However, in clinical practice, up to 10% of outpatients receiving statins report muscle pain (3,14).

CONCLUSION

3-Hydroxy-3-methyl glutaryl CoenzymeA reductase inhibitors or statins as highly efficacious agents for the lowering of low-density lipoprotein-cholesterol (LDL-C) revolutionized treatment of hypercholesterolemia, a long established risk factor for premature coronary heart disease.

Statins not only exhibit a remarkely high benefit to risk ration, but are equally characterized by a safety profile with excellent tolerance.

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