ΙΠΠΟΚΡΑΤΕΙΑ 1999, 3, 4: 171-176

ΠΡΩΤΟΤΥΠΗ ΕΡΓΑΣΙΑ

HMG-Co-A reductase inhibitors in the treatment of hypercholesterolemic renal transplant recipients

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Abstract: The aim of this study was to compare the safety and efficacy of lovastatin and fluvastatin in the treatment of hypercholesterolemic (HCH) renal transplant recipients (RTR).

Fifty steady HCH RTR received either 20 mg/d lovastatin (Group A = 22 pts, mean age: 40 yrs) or 40 mg/d fluvastatin (Group B = 28 pts, mean age: 41 yrs) for a period of one year. Total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides(TG) were measured before and at the end of the 3rd and 12th month of treatment. Serum creatinine (Scr), SGOT, SGPT, CPK and total bilirubin (TB) were measured at the same time intervals. ANOVA for repeated measures and independent t test were used for statistical analysis.

The TC levels were 304.54±38.38 mg/dl, 234.95±38.12 mg/dl, 240.23±39.09 mg/dl and 323.25±49.61 mg/dl (p:NS), 263.74±38.05 mg/dl (p:0.01), 262.90± 31.39 mg/dl (p: 0.04), HDL-C levels were 43.83±11.23 mg/dl, 49.06±7.44 mg/ dl, 55.33±16.30 mg/dl and 46.08±12.77 mg/dl, 52.45±21.60 mg/dl, 55.33± 16.30 mg/dl, LDL-C levels were 214.22±41.59 mg/dl, 169.33±41.76 mg/dl, 159.56±35.12 mg/dl and 237.52±53.80 mg/dl, 182.50±43.02 mg/dl, 178.05 ± 28.47 mg/dl, TG levels were 191.59±59.92 mg/dl, 155.53±53.67 mg /dl, 142.95±48.57 and 188.29±63.09 mg/dl, 151.59±54.09, 156.54±53.27 mg / dl in the Group A and B at the measured time intervals respectively. In Group A serum TC (p=0.0001), LDL-C (p=0.025), and TG (p=0.002) levels and in Group B TC(p=0.0001), LDL-C (p=0.005) and TG (p=0.044) levels showed statistically significant (ss) fall at the end of 3rd and 12th month. Serum HDL-C did not show any significant change during time in either group. Serum total cholesterol levels of Group A were significantly lower than those of Group B at 3rd and 12th month of treatment. Scr levels remained stable and no change was noticed in CPK, SGOT, SGPT, TB in both groups.

Lovastatin and fluvastatin are safe and cause significant fall of serum TC, LDL-C and TG levels. This fall is evident from the first three months of treatment. Lovastatin causes a deeper fall of serum TC at the 3rd and 12th month than fluvastatin(ss). Both drugs have no significant effect on HDL-C levels.

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Complications of atherosclerotic vascular disease are common after renal transplantation[1,2]. The pathogenesis of atherosclerosis in renal transplant recipients is multifactorial. Hyperlipidemia, a possible predisposing factor, has high prevalence among these patients[3,4]. Unfortunately most of the hypolipemic agents have been connected with adverse effects.

Inhibitors of 3-hydroxy-3-methylglutaril coenzyme A (HMG-Co-A) reductase have been shown to be effective in reducing total cholesterol and LDL-cholesterol acting competitively and have gained a basic role in the treatment of renal transplant recipients' hypercholesterolemia[5-8]. The first drug of this category to be used was lovastatin and although it proved to be relatively safe it was connected with adverse effects on skeletal muscles in patients taking cyclosporine[9,10]. Fluvastatin, the first completely synthetic HMG-Co-A reductase inhibitor, has been used successfully to treat

Part of this paper was presented and discussed as a poster in the XXXVI ERA-EDTA Congress (Madrid, Spain 7th of September 1999)

hypercholesterolemia of RTR and has a very low incidence rate (<0.5%) of musculoskeletal side effects such as myopathy and rhabdomyolysis[11]. Lovastatin and fluvastatin, with different ways of metabolism[12,13] that affect their systemic concentration when given concomitantly with cyclosporine, have been used in our clinic in the treatment of hypercholesterolemic RTR. This retrospective analysis aims at the investigation of the safety, efficacy and the future use of these drugs.

PATIENTS AND METHODS

Fifty clinically stable renal transplant recipients who received lovastatin 20 mg/d (Group A, 22 pts) or fluvastatin 40 mg/d (Group B, 28 pts) for hypercholesterolemia (total serum cholesterol > 240 mg/dl) were studied retrospectively.

Patients' mean age was 40±10.41 years (range 21 – 59 years) in Group A (12 men) and 41±13.56 years (range 15 – 59 years) in Group B (16 men), while the mean time from transplantation was 2.67 and 2.74 years respectively (therapy was given at least one year after transplantation). All patients had followed a three month lipid-low cholesterol diet before starting taking hypolipidemic agents(30% lipids, 50% carbohydrates, 20% protein and cholesterol less than 300 mg/d). Lovastatin was given during the years 1995-6 and fluvastatin during 1997-8. During this period all patients had regular follow up at monthly intervals at the outpatient department of our clinic. Their primary renal disease was Chronic Glomerulonephritis (GN): 13, Interstitial Nephritis (IN): 4, Polycystic Kidney Disease (PKD): 4, Angitis:1, Analgesic Nephropathy (AN):1, Unknown Etiology (UE):5 in group A and GN: 8, IN: 4, PKD:3, UE:2, Angitis:1, AN:1, Diabetic nephropathy:2, Nephrosclerosis:1 in Group B. They had been on triple or quadruple sequential drug immunosuppression (methylprednisolone 0.10 – 0.08 mg/Kg BW/d, CsA 2-4 mg/Kg BW/d, and azathioprine 0.5-1.5 mg/Kg BW/d or MMF 5 – 15 mg/Kg BW/d. Nine patients of group A and seven of group B had received ALG as induction therapy). Five patients of group A and three of group B had proteinuria ranging from 0.25 g/24hour to 1.0g/24hour. There was no liver disease, myopathy, thyroid disease or pregnancy. All patients were advised to take a steady diet already discribed[5].

Total serum cholesterol, triglycerides, HDL-cholesterol, serum creatinine, blood urea, blood glucose, SGOT, SGPT, CPK, LDH, total bilirubin, uric acid, 24 hour urine protein before and on the 3rd and 12th month of treatment with the hypolipidemic agents were analyzed. All laboratory values were measured after a 12hour fast. LDL-cholesterol was measured indirectly by the Friedwald type (LDL-cholesterol= total cholesterol – 1/5 triglycerides)[14]. The laboratory methods used for the above measurements have already been described[5]. Increases of transaminases were considered notable when, by consecutive measurements, SGOT and/or SGPT was confirmed to be elevated to more than three times the upper limit of the normal range used by the laboratory. Increases in CPK were considered notable when, at any time during the follow up its levels raised to more than 10 times the upper limit of the normal range used by the laboratory.

ANOVA for repeated measures and independent t test were used for statistical analysis (statistical package SPSS, version 9.0 for WINDOWS). The differences considered to be statistically significant when $p< 0.05$.

RESULTS

Lipids: Lipid levels recorded at baseline, after 3 and 12 month treatment with lovastatin and fluvastatin are given in Table 1 and 2 respectively. Analysis of variance for repeated measures during time showed that there was a significant fall of total cholesterol, LDL-C and triglycerides in Group A (p=0.0001, p=0.025, p=0.002) and B (p=0.0001, p=0.005, p=0.044) respectively. HDL-C raised during time but the rise was not significant with either treatment. After three month treatment with lovastatin the fall of total cholesterol, LDL-C and triglycerides from baseline was 22.86%, 20.96% and 18.83% respectively. At the end of 12 month treatment the fall of total cholesterol, LDL-C and triglycerides from baseline was 21.12%, 25.52% and 25.39% respectively. After three month treatment with fluvastatin there was a fall of total cholesterol, LDL-C and triglycerides from baseline levels by 18.40%, 23.16% and 19.49% respectively. At the end of 12 month treatment with fluvastatin there was a fall of total cholesterol, LDL-C and triglycerides from baseline levels by 18.73%, 25.03 % and 16.86 respectively (Table 3). The levels of lipids at baseline were not different between group A and B. The levels of total cholesterol at the end of the 3rd and 12th month of treatment of group A were statistically significantly lower than the total

cholesterol levels of group B (independent t test, p=0.01 and p=0.04 respectively). Baseline lipid levels as well as the levels at the 3rd and 12th month of treatment of LDL-C, HDL-C and triglycerides compared between groups did not show significant difference.

Renal function: Serum creatinine, blood urea, uric acid of both groups at baseline and at the end of the 3rd and 12th month of treatment are given in tables 4 and 5. The results show that the renal function remained stable during the study period in both groups.

Creatine phosphokinase and Liver function: No significant change of CPK, SGOT, SGPT, LDH and total bilirubin levels at baseline and at the end of the 3rd and 12th month of treatment in both groups was noticed (Tables 4,5,6,7)

Table 1. Changes of serum total cholesterol, LDL-C, HDL-C and triglycerides before, at the 3rd and 12th month of treatment with lovastatin

	Cholesterol mg/dl	LDL-C mg/dl	HDL-C mg/dl	Triglycerides mg/dl
Before	304.54±38.38	214.22±41.59	43.84±11.23	191.59±59.92
3rd month	234.95±38.12	169.33±41.76	49.06±7.44	155.53±53.67
12th month	240.23±30.09*	159.56±35.12**	53.75±13.99	142.95±48.57***

ANOVA for repeated measures *p=0.0001, **p=0.025, ***p=0.002

Table 2. Changes of serum total cholesterol, LDL-C, HDL-C and triglycerides before, at the 3rd and 12th month of treatment with fluvastatin

	Cholesterol mg/dl	LDL-C mg/dl	HDL-C mg/dl	Triglycerides mg/dl
Before	323.25±49.61	237.52±53.80	46.08±12.77	188.29±63.09
3rd month	263.74±38.05	182.50±43.02	52.45±21.60	151.59±54.09
12th month	262.90±31.39*	178.05±28.47**	55.33±16.30	156.54±53.27***

ANOVA for repeated measures *p=0.0001, **p=0.025, ***p=0.002

Table 3. The per cent changes of total cholesterol, LDL-C, HDL-C and triglycerides after treatment with lovastatin and fluvastatin.

		Lovastatin treatment		Fluvastatin treatment	
		3rd month %	12th month %	3rd month %	12th month %
Total cholest.	↓	22.86	21.12	18.40	18.73
LDL-C	↓	20.96	25.52	23.16	25.03
HDL-C	↑	11.90	22.6	13.80	20.07
Triglycerides	↓	18.83	25.39	19.49	16.86

Table 4. Levels of serum creatinine, blood urea, uric acid, glucose and bilirubin before, at the 3rd and 12th month of treatment with lovastatin

	Creatinine mg/dl	Blood urea mg/dl	Uric acid mg/dl	Glucose mg/dl	Bilirubin mg/dl
Before	1.35±0.49	48.36±13.81	6.64±1.47	94.04±29.13	0.60±0.10
3rd month	1.26±0.46	50.13±17.19	6.50±1.37	92.09±14.28	0.61±0.14
12th month	1.30±0.49	52.90±13.91	6.75±1.39	97.76±33.93	0.63±0.18

Table 5. Levels of serum creatinine, blood urea, uric acid, glucose and bilirubin before, at the 3rd and 12th month of treatment with fluvastatin

	Creatinine mg/dl	Blood urea mg/dl	Uric acid mg/dl	Glucose mg/dl	Bilirubin mg/dl
Before	1.30±0.40	55.92±18.07	7.67±1.45	88.74±9.44	0.60±0.14
3rd month	1.40±0.43	55.96±22.67	7.38±1.69	85.51±14.51	0.67±0.22
12th month	1.40±0.55	60.36±19.65	7.60±1.88	85.90±17.85	0.73±0.26

Table 6. Levels of serum SGOT, SGPT, LDH and CPK, before, at the 3rd and 12th month of treatment with lovastatin

	SGOT iu/l	SGPT iu/l	LDH iu/l	CPK iu/l
Before	21.22±8.58	22.31±15.23	274.92±33.42	54.50±26.7
3rd month	0.04±5.71	22.04±10.94	304.40±74.84	52.38±15.60
12th month	20.57±6.47	20.71±13.58	294.25±38.68	65.41±29.55

Table 7. Levels of serum SGOT, SGPT, LDH and CPK, before, at the 3rd and 12th month of treatment with fluvastatin

	SGOT iu/l	SGPT iu/l	LDH iu/l	CPK iu/l
Before	20.44±6.38	20.59±7.00	277.75±37.32	47.20±27.56
3rd month	20.69±5.56	20.34±7.65	329.44±97.42	48.20±20.56
12th month	22.00±10.02	20.22±9.78	340.85±95.73	50.94±23.73

DISCUSSION

The present retrospective analysis demonstrated that, the HMG-CoA reductase inhibitors, lovastatin and fluvastatin reduced statistically significantly total and LDL cholesterol as well as triglycerides levels in renal transplant recipients treated with corticosteroids, AZA/or MMF and cyclosporine. At the same time there was a raise in HDL-cholesterol levels which was not significant. The major reduction in lipid levels was evident by the third month of treatment after which there was no practically further fall.

The reductions in total and LDL cholesterol levels in Group A were similar to those reported in patients who received lovastatin for 6 weeks at the dose of 20 mg/d (immunosuppression=steroids plus azathioprine) or 10 mg/d (immunosuppression = steroids + AZA or MMF + cyclosporine) for three months[5,15]. But the fall noticed in triglyceride and the rise in HDL cholesterol levels, similar to that reported in patients with primary hyperlipidemias and comparable lovastatin doses[6], was not found in the previously mentioned reports[5,15].

In group B the significant fall of total and LDL cholesterol and triglycerides levels was similar to that reported in patients who received fluvastatin for 14 weeks at the dose of 20 mg/d[7] or for 20 weeks at the dose of 20 – 40 mg/d[8]. In these reports there was no or small HDL cholesterol raise while we noticed an HDL cholesterol level elevation at a rate of 20% achieved at the end of the year but it was not statistically significant.

Comparing the results between lovastatin and fluvastatin (table 1,2,3) we found that there was no much difference as far as their efficacy. Their major action was already obvious at the end of the 3rd month of treatment in the cases of total cholesterol, LDL cholesterol and triglycerides while the rate of HDL cholesterol elevation at the end of the year was double of that found at the 3rd month of treatment. This HDL-C level rise was not statistically significant in both groups and this is possibly due to the small number of patients.

It is known that the hypolipemic effect of statins is related with the oral dose and the level achieved in the blood. Lovastatin plasma exposure increases 20fold when coadministered with cyclosporine A[16]. Lovastatin is mainly metabolized by the cytochrome P-450 3A4 (CYP 3A4) enzyme[17] and secondarily by the P- glycoprotein[18]. Cyclosporine is metabolized by the CYP 3A4 and causes the increase of lovastatin levels. Fluvastatin area under the plasma concentration time curve increases only 1.9 fold when the drug is coadministered with cyclosporine A[19]. Multiple enzymes are involved in the metabolism of fluvastatin with CYP 2C9 as the major one[20]. Conversely, although fluvastatin is a potent inhibitor of CYP 2C9, this effect is limited because of fluvastatin's rapid systemic clearance[21]. The statistically significant lower total cholesterol levels of group A at the 3rd and 12th month of treatment, when compared with those of group B at the same time, would be explained by the different way of metabolism of the two drugs and the use of cyclosporine as immunosuppressive agent which causes very high lovastatin plasma levels.

Liver function checked by serial measurements of SGOT, SGPT, LDH (Table 6,7) and bilirubin (Table 4,5) remained stable in both groups. The administration of lovastatin and fluvastatin for one year was not associated with signs of muscle damage, such as a tenfold rise of CPK, myalgias and leg pain. CPK levels remained in the normal range and did not change significantly at the time examined (Table 6,7).

Serum creatinine, blood urea and uric acid levels did not show significant change during the first year of treatment with either drug.

These drugs have been proved to be equally safe and effective in the treatment of hyperlipemic RTR in the above mentioned doses. But the experience has shown that it is not always achievable to normalize serum lipid levels using low doses of statins as those we usually prescribe. We can discriminate the patients according to their response to those who are responders (normalize their total cholesterol levels), to those who present a significant fall of total cholesterol levels without normalizing it (partial responders, a fall of about 20%) and those who do not present significant fall of total cholesterol levels (no responders, a fall of about 10%).

It is known that the side effects of certain HMG-Co-A reductase inhibitors increase with increased systemic concentrations of them when coadministered with other drugs. It has also been reported that the incidence of musculoskeletal side effects of lovastatin increase up to 28% when cyclosporine is given at the same time[6]. On the other hand fluvastatin has a low potential for metabolic drug-drug interactions as compared with other HMG-Co-A reductase inhibitors.

Targeting at the serum lipid normalization of partial and no responders we have to augment the dose of these hypolipemic agents or to add other drugs. Having in mind that fluvastatin has different way of metabolism from cyclosporine and a rapid systemic clearance we feel safe and prefer to use this drug the last years instead of lovastatin. Possibly it would be justified to try higher doses of fluvastatin in RTR who are partial responders to fluvastatin at the dose of 40 mg/d. On the other hand there is already the positive experience of the combination of fluvastatin (40 mg/d) with gemfibrozil (600 mg/d)

in the treatment of hyperlipemic RTR who are no responders to fluvastatin[22].

ΠΕΡΙΛΗΨΗ

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Σκοπός της εργασίας αυτής ήταν να συγκρίνουμε την αποτελεσματικότητα και την ασφάλεια της λοβαστατίνης και της φλουβαστατίνης στη θεραπεία μεταμοσχευμένων ασθενών με υπερχοληστερολαιμία.

Πενήντα σταθεροποιημένοι μεταμοσχευμένοι ασθενείς με υπερχοληστερολαιμία πήραν ή λοβαστατίνη 20 mg/d (Ομάδα Α = 22 ασθενείς, ηλικίας 40 ετών) ή φλουβαστατίνη 40 mg/d (Ομάδα Β = 28 ασθενείς, ηλικίας 41 ετών) για ένα χρόνο. Η ολική χοληστερόλη(TC), η HDL-χοληστερόλη (HDL-C), η LDL-χοληστερόλη(LDL-C) και τα τριγλυκερίδια(TG) μετρήθηκαν πριν, 3 και 12 μήνες από την έναρξη της θεραπείας. Επίσης στις ίδιες χρονικές στιγμές μετρήθηκαν η κρεατινίνη του ορού, οι SGOT, SGPT, CPK, και η ολική χολερυθρίνη(TB) του ορού. ANOVA για επαναλαμβανόμενες μετρήσεις και t test για μη ζεύγη τιμών χρησιμοποιήθηκαν για τη στατιστική ανάλυση.

Τα επίπεδα της TC ήταν 304,54±38,38 mg/dl, 234,95±38,12 mg/dl, 240,23±39,09 mg/dl και 323,25±49,61 mg/dl(p=NS), 263,74±38,05 mg/dl (p=0,01), 262,90±31,39 mg/dl(p=0,04), τα επίπεδα της HDL-C ήταν 43,83± 11,23 mg/dl, 49,06±7,44 mg/dl, 55,33±16,30 mg/dl και 46,08±12,77 mg/dl, 52,45±21,60 mg/dl, 55,33±16,30 mg/dl, τα επίπεδα της LDL-C ήταν 214,22±41,59 mg/dl, 169,33±41,76 mg/dl, 159,56±35,12 mg/dl και 237,52±53,80 mg/dl, 182,50±43,02 mg/dl, 178,05±28,47 mg/dl, τα επίπεδα των TG ήταν 191,59±59,92 mg/dl, 155,53±53,67 mg/dl, 142,95±48,57 mg/dl και 188,29±63,09 mg/dl, 151,59±54,09 mg/dl, 156,54±53,27 mg/dl στην ομάδα Α και Β στα προαναφερθέντα χρονικά διαστήματα αντίστοιχα. Στην Ομάδα Α τα επίπεδα των TC (p=0,0001), LDL-C (p=0,025) και των TG(p=0,002) και στην Ομάδα Β TC (p=0,0001), LDL-C (p=0,005) και TG (0,004) έδειξαν στατιστικά σημαντική πτώση στο τέλος του 3ου και 12ου μήνα. Η HDL-C δεν παρουσίασε σημαντική μεταβολή στη διάρκεια της θεραπείας και στις δυο ομάδες ασθενών. Τα επίπεδα της TC ήταν σημαντικά χαμηλότερα στην ομάδα Α συγκριτικά με την ομάδα Β τον 3ο και 12ο μήνα. Τα επίπεδα της Scr παρέμειναν σταθερά και δε διαπιστώθηκε μεταβολή στα επίπεδα των CPK, SGOT, SGPT, TB κατά τη διάρκεια της θεραπείας στις ομάδες Α και Β.

Η λοβαστατίνη και η φλουβαστατίνη είναι ασφαλή φάρμακα και προκαλούν σημαντική των επιπέδων της TC, LDL-C και των TG στον ορό. Η πτώση αυτή είναι εμφανής από τους 3 πρώτους μήνες της θεραπείας. Η λοβαστατίνη προκαλεί μεγαλύτερη πτώση της TC του ορού τον 3ο και 12ο μήνα συγκριτικά με την φλουβαστατίνη. Και τα δυο τα φάρμακα δεν προκαλούν σημαντική μεταβολή στα επίπεδα της HDL-C.

REFERENCES

1. Ibels LS, Srewart JH, Mahony JF, Neale FC, Sheil AGR. Occlusive arterial disease in ureamic and haemodialysis patients and renal transplant recipients. Q J Med 1977;46:197
2. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med 1988;84:985
3. Kasiske BL, Umen AJ. Persistent hyperlipidemia in renal transplant patients. Medicine (Baltimore) 1987;66:309
4. Ponticelli C, Barbi GL, Cantalupi A, et al. Lipid disorders in renal transplant recipients. Nephron 1978;20:189
5. Vergoulas G, Miserlis Gr, Solonaki F, et al. Treatment of hypercholesterolemia of renal allograft recipients with lovastatin. Hippokratia 1997;1:151-158
6. Tobert JA. Efficacy and long term-adverse effect pattern of lovastatin. Am J Cardiol 1998;62:28J-34J
7. Goldberg RB, Roth D. A preliminary report of the safety and efficacy of fluvastatin for hypercholesterolemia in renal transplant patients receiving cyclosporine Am J Cardiol 1995;76:107A-109A
8. Holdaas H, Hartmann A, Stenstrom, et al. Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporine. Am J Cardiol 1995;76:102A-106A
9. Norman DJ, Illingworth DR, Munson J, Hosenpud J. Myolysis and acute renal failure in heart-transplant recipient receiving lovastatin. N Engl J Med 1988;318:46
10. East C, Alivizatos PA, Grundy SM, Jones PH, Farmer JA. Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. N Engl J Med 1988, 318:47
11. Peters TK, Mehra M, Muratti EN. Efficacy and safety of fluvastatin in hypertensive patients. Am J Hypertens 1993;6:340S-345S
12. Michalets EL. Reviews of therapeutics. Update: Clinically Significant cytochrome P-450 drug interactions. Pharmacotherapy 1998;18:84-112
13. Fischer V, Johanson L, Heitz F, et al. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor Fluvastatin: Effect on human cytochrome P-450 and implications for metabolic drug interactions. Drug Met Dispos 1999;27:410-416
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-504

15. Kasiske BL, Tortorice KL, Heim-Duthoy L, Goryance JM, Rao KV. Lovastatin treatment of hypercholesterolemia in renal transplant patients. Transplantation 1990;49:95-100.
16. Olbricht C, Wanner C, Eisenhauer T, et al. Accumulation of lovastatin but not pravastatin in the blood of cyclosporine treated kidney graft patients after multiple doses. Clin Pharmacol Ther 1997;62:311-321.
17. Wang RW, Kari PH, LU AYH, Thomas PE, Guengerich FP and Vyas KP. Biotransformation of lovastatin, IV. Identification of cytochrome P450 3A proteins as the major enzymes responsible for the oxidative metabolism of lovastatin in rat and human liver microsomes. Arch Biochem Biophys 1991;290:355-361
18. Dimitroulakos J and Yeger H. HMG-CoA reductase mediates the biological effects of retinoic acid on human neuroblastoma cells: Lovastatin specifically targets P-glycoprotein expessing cells. Nature Med 1996;2:326-333
19. Goldberg R and Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. Transplantation (Baltimore) 1996;62:1559-1564
20. Dain JG, Fu E, Gorski J, Nikoletti J, Scallen TJ. Biotransformation of fluvastatin sodium in humans. Drug Metab Dispos 1993;21:567-572
21. Transon C, Leemann T and Dayer P. In vitro comparative inhibition of major human drug metabolising cytochrome P 450 isoenzymes. (CYP 2C9, CYP2D6, CYP3A4) by HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1996;50:209-215
22. Vergoulas G, Miserlis Gr, Solonaki F, et al. Combined treatment of hypercholesterolemia of renal transplant allograft recipients with fluvastatin and gemfibrozil(υπό δημοσίευση στο Transplant International.

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