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Research Article

STUDY OF DRUG-DRUG INTERACTION ON THE MANAGEMENT OF HYPERLIPIDEMIC DISEASE: SIMVASTATIN AND EZETIMIBE

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ABSTRACT

This study was designed to investigate the effects of combination of ezetimibe and simvastatin on lipoproteins in patients with mixed dyslipidemia. Among the 482 patients screened 465 who met the inclusion criteria after 6weeks on a strict diet therapy were grouped into three treatment groups. The inclusion criteria were mixed dyslipidemia with a high triglyceride level (200-499 mg per 100ml) and a total cholesterol level more than 200mg per 100ml. Retrospective study was conducted on dyslipidemic patients receiving ezetimibe (10mg) alone, simvastatin (20mg) alone, and combination of simvastatin (20mg) and ezetimibe (10mg) daily for 24weeks. After 24 weeks treatment,(Tc, Tg, LDL)was found significantly decreased and HDL level increased in the combination therapy (Simvastatin and ezetimibe) than monotherapy. From the result it is concluded that combination therapy may be considered as an optimal treatment option for patients with mixed dyslipidemia.

Keywords: Simvastatin, Ezetimibe, Retrospective study.

INTRODUCTION

Retrospective and prospective are the two types of drug use evaluation. In prospective (concurrent) review patients planned drug therapy evaluated before a medication is administered. During a retrospective, drug therapy is reviewed after the patient has completed a course of therapy [(1)].

Plasma lipid levels are decreased by diet restriction or by drugs simvastatin, atorvastatin etc.. High serum levels of LDL and VLDL are caused atherogenic while high HDL level considered as protective effect. Hyperlipoproteinemias are incriminated in the pathogenesis of atherosclerosis. Elevation of plasma LDL cholesterol especially when combined with reduced HDL, is associated with increased risk of atherosclerotic arterial disease[(2)].

The Reduction of elevated serum total cholesterol (Tc) and low-density lipoprotein cholesterol (LDL-c) reduces the risk of coronary artery disease, resulting in a decrease in cardiovascular morbidity and mortality[(3)].

Lesser than 130 mg/dl of LDL, 200 mg/dl of Tc, 200 mg/dl of triglycerides and more than 60 mg/dl of HDL are the desirable level, To achieve this goal high statin doses may be necessary which increases its adverse effects. Given that statin monotherapy may be insufficient for the desirable reduction in LDL levels, a combination of lipid lowering agents has become frequent in clinical practice[(4)].

The objective of the study to investigate the effects of combination of ezetimibe and simvastatin on lipoproteins, in patients with mixed dyslipidemia.

MATERIALS AND METHODS

The retrospective study was conducted at Medzon G.S.Hospital, Chennai to investigate the effect of ezetimibe and simvastatin on dyslipidemic patients. The study was conducted on dyslipidemic patients who were receiving simvastatin treatment between the years of 2008 to 2012. Clinical information and laboratory parameters were collected by reviewing medical records.

Inclusion criteria of patients were mixed dyslipidemia with high triglyceride level 200-499 mg/dl and total cholesterol level more than 200 mg/dl. Also patients should be on the treatment of fixed dose of simvastatin for 6 months. Exclusion criteria were 1) the type or dose of simvastatin was switched during the period. 2) Patients used other lipid lowering therapy during the period. 482patients were screened between the years of 2008-2012 and 465patients were met requirement of inclusion criteria and they were divided into 3groups.

Group 1patients was received a monotherapy with of 10 mg of ezetimibe (150 patients) 0rally, Group 2 received alone 20mg of simvastatin (n=150) orally. Group 3 was administered combination treatment with ezetimibe (10mg) and simvastatin (20mg) orally (n=150).

RESULT AND DISCUSSION

In this study, the effect of ezetimibe10mg plus 20 mg simvastatin combination therapy was evaluated in patients with mixed dyslipidemia. Seven patients were dropped out from first group due to non compliance and five patients from second group and three from third group were excluded because of the patient's refusal. The percentage change from the baseline in LDL levels, the primary outcome variable, was significantly greater with ezetimibe plus simvastatin than with ezetimibe or simvastatin alone. There were significant reductions of Total cholesterol levels observed after treatments. HDL cholesterol level was not much affected after either combination of ezetimibe and simvastatin and ezetimibe or simvastatin alone therapy.

.Simvastatin belongs to HMG COA REDUCTASE inhibitors which inhibit HMG-COA involved in the formation of mevalonic acid (in liver cholesterol denovo synthesis) which results in decreased hepatic cholestral synthesis. This leads to increased synthesis of high affinity LDL-receptors (up regulation)on the surface of liver cells leading to increased clearance (uptake)of cholesterol rich plasma LDL[5,6]. Statin monotherapy be insufficient for the desirable reduction in LDL levels, a combination of lipid-lowering agents has become frequent in clinical practice. In particular, statin and ezetimibe combination has been shown to be very effective in reducing total and LDL-cholesterol levels.

Table 1: Effect of Ezetimibe Monotherapy On Various Lipoprotein Levels

Lipoprotein mg /dl	Ezetimibe (10 mg)			
	Base	6th week	12th Week	24th Week
T-c	236.3 ± 0.08057	205.2 ± 0.1324**	172.6 ± 0.1282**	195.6 ± 0.04928**
T-G	177.6 ± 0.219	167.1 ± 0.0337**	163.3 ± 0.0411**	146.2 ± 0.07195**
HDL-c	56.74 ± 0.6062	57.06 ± 0.5986**	57.16 ± 0.1131**	58.94 ± 0.9180**
LDL-c	144.3 ± 0.06259	136.13 ± 0.06244**	124.64 ± 0.0729**	113.2± 0.2311**

T-c-Total cholesterol,T-g-Triglycerides, HDL-c – High density Lipoprotein, LDL- c, Low density Lipoprotein. Comparisons were made between: Base and 6th, 12th and 24th Week.
Symbol represents the statistical significance done by ANOVA. * P<0.001.

The primary objective was to compare the change in LDL-C, TC and Tg levels in the three groups from the baseline with week 6th, 12thand 24thweeks. Lipoproteins like HDL levels were also analyzed. The effect of treatment was significant when p-value was less than 0.05 (one way ANOVA).

Ezetimibe is a specific cholesterol absorption inhibitor that acts at the brush border of the small intestine, blocking the

Table 2: Effect of Simvastatin monotherapy on various lipoprotein levels in blood

S no	LIPOPROTEIN mg/dl	Simvastatin (20 mg)			
		Base	6th week	12th week	24th week
1.	T-c	233±0.1546	200±0.1744**	196±0.1309 **	184.7±0.1399 **
2.	T-G	292.5±0.2064	275.5±0.2504 **	249.5±0.2164 **	234.6± 0.1675**
3	HDL-c	40.53±0.05299	41.53 ±0.04289 **	44.53 ±0.08169 **	44.41 ± 0.06354 **
4	LDL-c	137.4±0.06956	134.2 ±0.07656**	128.6±0.08416**	97.71±0.08249**

T-c-Total cholesterol, T-g-Triglycerides, HDL-c – High density Lipoprotein, LDL- c, Low density Lipoprotein.
Comparisons were made between: Base and 6th, 12th and 24thWeek.
Symbol represents the statistical significance done by ANOVA. * P<0.001.

Table 3: Effect of Ezetimibe and Simvastatin Combination on Various Lipoprotein Levels

Lipoprotein mg /dl	Ezetimibe (10 mg) + Simvastatin (20 mg)			
	Base	6th week	12th Week	24th Week
T-c	252.4 ± 0.5337	218.4 ± 0.5017**	175.4 ± 0.4937	145.9 ±0.09761
T-G	198.6 ± 0.33419	168.6 ± 0.38419**	135.9 ± 0.3238**	108.8 ±2.926**
HDL-c	56.06 ± 0.5986	56.86 ± 0.4819**	57.12 ± 0.4410**	58.4 ±0.5013**
LDL-c	144.3 ± 0.06259	128.9 ± 0.4480**	107.5 ±0.7457**	68.59 ±0.5267**

T-c-total cholesterol, T-g-Triglycerides, HDL-c – High density Lipoprotein, LDL- c lowdensity Lipoprotein. Comparisons were made between: Base and 6th,12th and 24th Week.
Symbol represents the statistical significance done by ANOVA. * P<0.001.

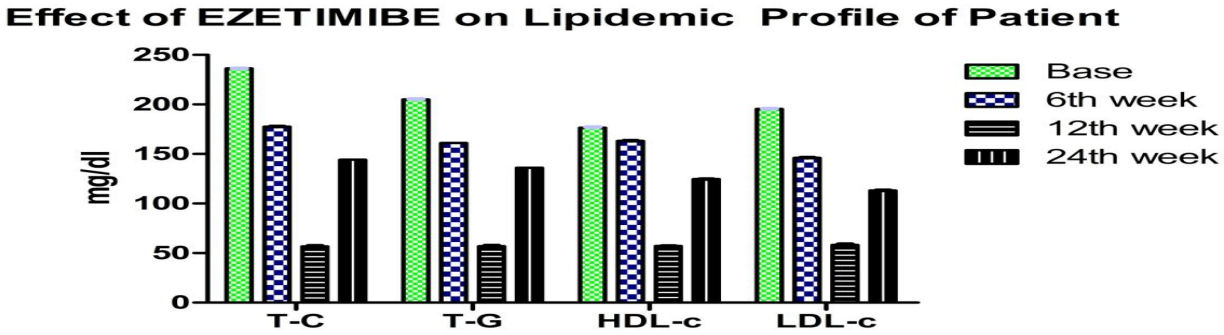
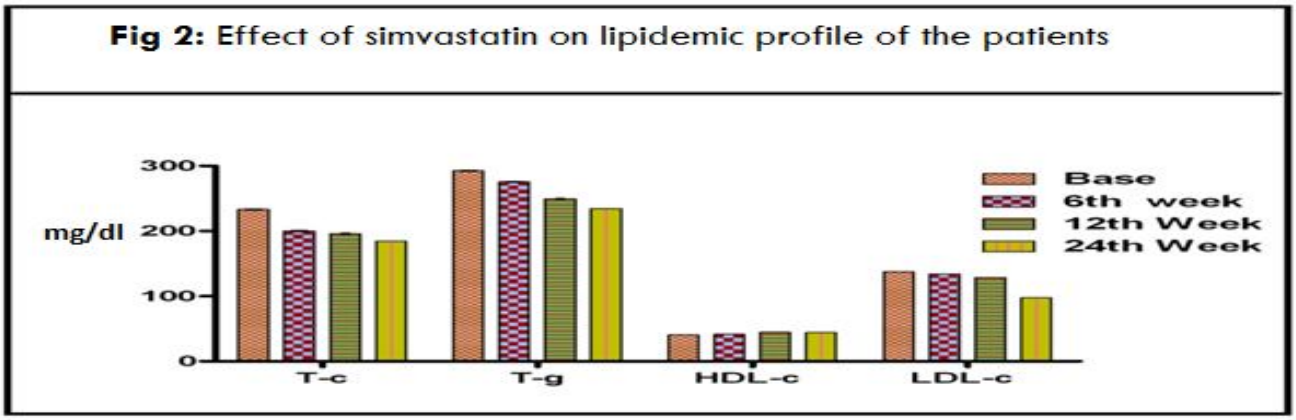


Fig 1: Effect of ezetimibe on lipidemic profile of the patients



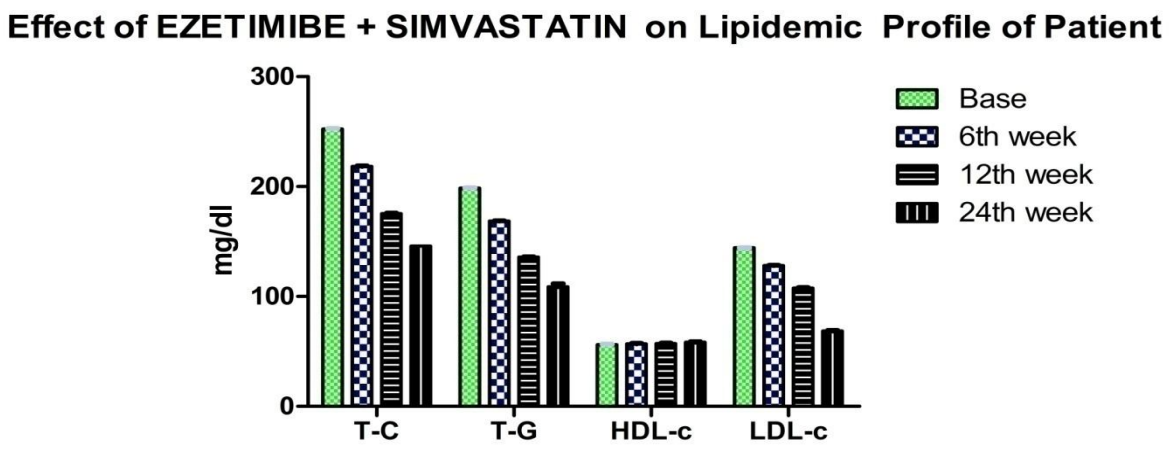


Fig 3: Effect of ezetimibe and simvastatin on lipidemic profile of the patients

absorption of dietary and biliary cholesterol and plant sterols, resulting in intracellular cholesterol depletion via the Niemann-Pick C1-like transporter (bind with mucosal transporter) .Leading to decreased delivery of dietary and biliary cholesterol to the liver. Reduction of hepatic c1holesterol stores causes increase in LDL receptors on the hepatocytes (upregulation) and an increased LDL cholesterol clearance from the blood [7].

Adding ezetimibe to statin therapy induces a significant reduction in LDL levels compared with achieved by doubling the dose of statins .This combination particularly useful in patients who do not tolerate large doses of statins.

CONCLUSION

The combination therapy with ezetimibe plus simvastatin produced a greater reduction in LDL-c levels than simvastatin and ezetimibe monotherapies in dyslipidemic patients. Along with the reduction of LDL-c, total cholesterol and triglycerides were also controlled with the combination therapy without adverse events. Thus a combination therapy of simvastatin and ezetimibe would be considered an optimal treatment option for patients with mixed dyslipidemia.

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REFERENCE

1. G. Parthasarathi, Karin N Hansen, Milap C Nahata. A textbook of clinical pharmacy practice-Orient longman, Hyderabad, 2004; 8; 84-90.
2. R. S. Satoskhar, N. N Rege, S.D. Bhandarkar. Pharmacology and pharmacotherapeutics, popular prakashan, Revised 22nd edition, 582-586.
3. Teddy kosoglou, ingo Meyer, Enrico p .veltri, paul statkevich, Bo yang, yali zhu, Lillian Mellars, Stephen E.Maxwelll, james E.patrick, David L. cutler, vijay k. Batra, and melton B.affrime. Pharmacodynamic interaction between the new selective cholesterol absorbtion inhibitor ezetimibe and simvastatin. British journal of clinical pharmacology 2002;54, 309-319.
4. Lucia MA karter,Marcel C Batista,Sandra RG Ferraira studied synergistic effect of Simvastatin and ezetimibe on lipid and pro-inflammatory profiles in pre-diabetic subjects.Diabetol Metab Syndr, 2010; 2; 34.
5. Chin-Feng Hsuan, Thung–lip Lee, Hsiu-Ling Chang, Wei-Kung Tseng, and Chau–Chung Wu studied, A Retrospective Study of Statin use and its EffectiveLness in Taiwanese;Acta Cardiol Sin;2009; 25;18-25.
6. Goodman and Gilmans, The Pharmacological Basis Of Therapeutics. Ninth Edition. Mcgraw-Hill, International Edition.
7. Chen-Fang Lin et al studied,Impact of Ezetimibe Coadministered With Statins on cardiovascular Events Following Acute Coronary Syndrome: A 3-Year Population-Based *Retrospective* Cohort Study in Taiwan. Clinical therapeutics; 2011; 33 (9);100-106

