ORIGINAL ARTICLE

Long Term Efficacy and Safety of A Generic Atorvastatin in Usual Clinical Care Setting

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SUMMARY

A multicentre study was conducted to assess the long term efficacy and safety of a generic atorvastatin in the treatment of primary hypercholesterolaemia. Eighty five patients who received 10mg or 20mg of atorvastatin for 8 weeks depending on target cholesterol goal were followed up by their own physicians and had final evaluation at 52 weeks. Reduction in mean low density Lipoprotein (LDL-C) was 36.5%, 37.9% and 32.2% at weeks 4, 8 and 52 respectively. LDL-C target was maintained in 81% and 69% of patients at week 8 and 52 respectively without drug related serious adverse events. Generic atorvastatin is safe and effective in usual clinical care setting.

KEY WORDS:

Hypercholesterolaemia, Coronary Heart Disease (CHD), 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, Real life clinical setting, Long term efficacy

INTRODUCTION

Elevated serum low density lipoprotein cholesterol (LDL-C) plays a significant role in the development of atherosclerosis and subsequent Coronary artery disease (CAD). The current standard of pharmacological intervention for the reduction of LDL-C is 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors or commonly referred to as statins[1-5].

The advent of statins has revolutionized the treatment of hypercholesterolemia. Statins are the most commonly prescribed agents for the treatment of hypercholesterolemia because of their efficacy and excellent tolerability. In large long-term trials, atorvastatin produced greater reductions in total cholesterol, LDL-C and triglyceride levels compared with other HMG-CoA reductase inhibitors[6]. Though atorvastatin is highly popular in markets with minimal barrier of access to its use, in Malaysia the high cost of the innovator drug has precluded its wider use and Atorvastatin merely ranked twenty-ninth on the Malaysian drug use list[7]. The availability of a cheaper generic atorvastatin would improve access to the drug.

We conducted an 8-week trial of the generic atorvastatin in patients with primary hypercholesterolaemia. In the study, atorvastatin reduced the mean LDL-C by 36.6% at 4 weeks and 37.5% at 8 weeks[8]. To determine the long-term efficacy and tolerability of this generic atorvastatin we extended the follow-up of the patients to 52 weeks.

MATERIALS AND METHODS

This is a multi-center, prospective, open-labeled single arm study conducted in the usual clinical care setting to assess the efficacy of a generic atorvastatin in the treatment of Primary Hypercholesterolemia for 12 months. The study was approved by the Research ethics committee and informed consent was obtained from all patients.

One hundred and twenty two patients from 14 participating centres were enrolled into an 8-week study. The 114 patients who completed the study were invited to continue in the trial for 52 weeks.

Initial recruitment consisted of patients with primary hypercholesterolaemia above the age of 18 years and who did not benefit from 12 weeks of Therapeutic Life Style changes. The LDL-C level for inclusion ranged from 2.6 to 7.5mmol/l depending on the 10-year risk of coronary heart disease (CHD) and the presence of CHD or CHD equivalent conditions. Patients with known hypersensitivity or muscle toxicity to statins, family history of hereditary muscle disorders, uncontrolled diabetes mellitus, treatment with lipid lowering drugs in the previous 6 weeks, elevated liver enzymes to more than 1.5 times above the upper limit of normal (ULN), elevated serum Creatine Phosphokinase (CPK) more than 5 times ULN, serum creatinine above 1.2 times ULN and serum triglycerides of more than 5.56mmol/L at baseline were excluded from the study.

After initial screening, patients underwent a baseline evaluation and all eligible patients were given a generic atrovastatin (Storvas by Ranbaxy Laboratories) 10 mg Tablets once daily for four weeks and increased to 20mg for the next 4 weeks if the target LDL-C was not achieved. The LDL-cholesterol targets were adopted from the "The National Cholesterol Education Program (NCEP-ATP III)" Guidelines. (14) The targets for patients with CHD or CHD risk equivalent, 2 or more major risk factors for CHD and 0-1 risk factor were < 2.6mmol/L, < 3.4mmol/L and < 4.1 mmol/L respectively.

Patients who completed 8 weeks of the trial were supplied with the study medication for another 44 weeks at the same dose they received at the end of the initial phase of the study and were followed up by their usual physicians. At the end of the study period, they returned for a final study visit at respective study sites. During this visit, compliance to treatment was ascertained by the number of missed doses of

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study medication as reported by the patient. Concomitant medications including study specific prohibited medication and major adverse events were also recorded. Patients underwent a brief physical examination and blood samples were drawn for lipid profile, liver function test and CPK. All laboratory measurements were performed at a central laboratory.

Efficacy analysis was performed on 85 patients who completed the 52 weeks of the study. This population is a subset of the one hundred and fourteen patients who completed the first 8weeks of the study and excluded those who did not consent to continue in the extended phase of the study and those who did not attend the final study visit for efficacy assessment. Safety report was based on safety set which included all the 122 patients who received at least one dose of study treatment.

RESULTS

Of the 114 patients who completed the first 8 weeks of the study, 85 were evaluable at 1 year. The trial profile is shown in Figure I.

Of the 114 patients, 29 did not participate in the study. Eight were lost to follow up and 5 patients were transferred to other centres. One patient was withdrawn because of pregnancy. Seven patients discontinued the study medication due to adverse events. Another 8 patients did not consent to participate in the extended phase.

The baseline characteristics of 85 patients who were evaluated in the study are shown in Table I

Compliance:
Good compliance (defined as consumption of at least 80% of the prescribed tablets) was achieved throughout the study with 99% of the patients compliant at 4 weeks, 96% at 8 weeks and 95% at 52 weeks for per protocol population.

Primary end-point
The LDL-C results are shown in Table II.

The mean LDL cholesterol was significantly reduced by 36.45% at 4 weeks, 37.87% at 8 weeks and 32.16% at 52 weeks compared with baseline (p-value <0.0001). The mean percentage change of LDL cholesterol at 52 weeks was an increase by 10.67% compared with week 8 but this increase was not statistically significant (p-value of 0.062).

Eighty two percent of patients achieved LDL-cholesterol target at 4 weeks and 81% continued to maintain the target at week 8. However only 69% maintained that target value at week 52. (Table 3). The 'CHD or CHD risk equivalent group' was better at maintaining their target LDL-C in the long term. Their attainment of target LDL-C goal was 71%, 74% and 71% for weeks 4, 8 and 52 respectively. In '0-1 risk factor group' the percentage of patients attaining the target level at 4 weeks and 8 weeks was high (both 95%) but only 67% of them maintained the target LDL-C levels at 52 weeks.

Secondary end-points
The total cholesterol and triglyceride levels were significantly reduced compared with baseline. (Table 4). The increase in total cholesterol and triglycerides at week 52 compared to week 8 though minimal are statistically significant. The HDL-cholesterol increased by 5.63% (0.05mmol/l) from week 8 to week 52 though there was a slight decrease during the first 8 weeks of the study.

Safety evaluation
Safety was evaluated in 122 patients who took at-least one dose of the study medication.

There were 5 serious adverse events reported during the first 8 weeks of the study and none was assigned by investigators to be causally related to the study drug. One patient became pregnant during her participation in the study and has given birth to a normal child since.

Seventy-one adverse event episodes were reported in 51 patients. Of these seventy one episodes 15.5% were thought to be related to study drug. These adverse events were abdominal pain, diarrhoea, arthralgia, musculoskeletal pain, dizziness, headache and pruritus. No deaths, acute coronary events, cardiac revascularization, acute cerebral events, rhabdomyolysis or acute liver failure were reported.

Adverse events which were considered to be investigational product related were myalgia in two patients, lethargy in one patient and joint pain in another patient, all of which got resolved after stopping the study drug.

During the first 8 weeks of the study, CPK was increased above baseline in 4 patients. The maximum CPK recorded was 650U/L, 2.2 times above the upper limit of normal (ULN) in one patient. The patient was asymptomatic and did not require any dose adjustment of the study drug. Alanine transaminase (ALT) was increased from baseline in 2 patients and the maximum elevation was 1.4 times above ULN. No patients had to withdraw the study drug due to adverse effects.

Table I: Demographics and Baseline Characteristics of Trial Patients

Characteristics	
Age, years, median (range)	55 (27-76)
Male:Female, N (ratio)	49:36 (1.4 : 1)
Malay:Chinese:Indian:Others (%)	53: 33: 12: 2
Major risk factors for CHD that modify LDL Goal	
Men≥ 45 years or women ≥55 years, N (%)	54 (64)
Hypertension, N (%)	67 (79)
Diabetes mellitus, N (%)	31 (36)
Cigarette smoking, N (%)	10 (12)
Low HDL cholesterol, N (%)	10 (12)
Family history of premature CHD, N (%)	11 (13)
Serum Plasma Chemistry	
ALT in U/L, mean (SD)	24.76 (9.65)
AST in U/L, mean (SD)	24.05 (6.34)
Total Bilirubin in µmol/L, mean (SD)	11.55 (4.12)
CPK in U/L, mean (SD)	120.86 (80.42)
Total Cholesterol in mmol/L, mean (SD)	6.46 (1.09)
HDL Cholesterol in mmol/L, mean (SD)	1.35 (0.33)
LDL Cholesterol in mmol/L, mean (SD)	4.37 (0.96)
Triglycerides in mmol/L, mean (SD)	1.60 (0.64)

Table II: LDL-cholesterol by Study visit

	Baseline	Week 4	Week 8	Week 52
LDL Cholesterol, mmol/L				
N	85	85	85	85
Mean (SD)	4.37 (0.96)	2.72 (0.68)	2.65 (0.58)	2.91 (0.94)
Mean change from Baseline (SD)	-	-1.65 (0.86)	-1.71 (0.79)	-1.46 (0.95)
95% CI		-1.84, -1.46	-1.88, -1.54	-1.66, -1.25
p-value	-	<0.0001**	<0.0001**	<0.0001**
Mean percentage change from Baseline (SD)	-	-36.45 (15.00)	-37.87 (12.70)	-32.16 (19.73)
95% CI		-39.68, -33.21	-40.61, -35.13	-36.42, -27.91
p-value	-	<0.0001*	<0.0001*	<0.0001*
Mean of change from Week 8	0.00	0.00	0.00	0.26
Mean percentage change from Week 8	0.00	0.00	0.00	10.67
p-value of Mean percentage change compared to Week 8	NA	NA	NA	0.062*

* Wilcoxon sign rank test SD = standard deviation

Table III: Distribution of patients achieving the NCEP ATP III goals by risk group

LDL-C Goal according to risk factor	Week 4 (N=85) Achieved the goal			Week 8 (N=85) Achieved the goal			Week 52 (N=85) Achieved the goal		
	Total	No	%	Total	No	%	Total	No	%
CHD or CHD risk equivalent: LDL <2.6	38	27	71	38	28	74	38	27	71
Multiple (2+) risk factor: LDL<3.4	26	23	88	26	21	81	26	18	69
0-1 risk factor: LDL<4.2	21	20	95	21	20	95	21	14	67
Total	85	70	82	85	69	81	85	59	69

Table V: Secondary end-points by study visit

	Baseline	Week4	Week8	Week 52
Total Cholesterol, mmol/L				
Mean (SD)	6.46(1.09)	4.60 (0.84)	4.53 (0.74)	4.88 (1.07)
Mean change from Baseline (SD)		-1.86	-1.93	-1.58
		(0.97)	(0.90)	(1.05)
95% CI		-2.07,	-2.12,	-1.81,
		-1.65	-1.73	-1.35
Mean percentage change from Baseline (SD)		-27.90 (12.18)	-28.97 (11.27)	-23.70 (15.03)
95% CI		-30.53,	-31.40,	-26.94,
		-25.27	-26.54	-20.46
p-value compared to baseline		<0.0001*	<0.0001*	<0.0001*
Triglycerides, mmol/L				
Mean(SD)	1.60(0.64)	1.29 (0.52)	1.32(0.56)	1.41 (0.56)
Mean change from Baseline (SD)		-0.31(0.44)	-0.28(0.48)	-0.19(0.55)
95% CI		-0.40,	-0.38,	-0.31,
		-0.22	-0.17	-0.075
Mean percentage change from Baseline (SD)		-15.53	-13.43	-6.44
		(24.76)	(26.92)	(31.96)
95% CI		-20.88,	-19.24,	-13.33,
		-10.19	-7.63	0.45
p-value compared to baseline		<0.0001*	<0.0001*	0.0277*
HDL Cholesterol, mmol/L				
Mean (SD)	1.35(0.33)	1.29 (0.29)	1.27 (0.34)	1.32 (0.29)
Mean change from Baseline (SD)		-0.07 (0.24)	-0.09(0.27)	-0.04(0.22)
95% CI		-0.12,	-0.15,	-0.084,
		-0.014	-0.031	0.0095
Mean percentage change from Baseline (SD)		-2.93	-5.25	-1.33
		(18.74)	(19.51)	(16.51)
95% CI		-6.97,	-9.45,	-4.89,
		1.11	-1.04	2.23
p-value of mean change compared to baseline	<0.003*	<0.0001*	0.0469**	

* Wilcoxon sign rank test
SD = standard deviation
**Paired t-test

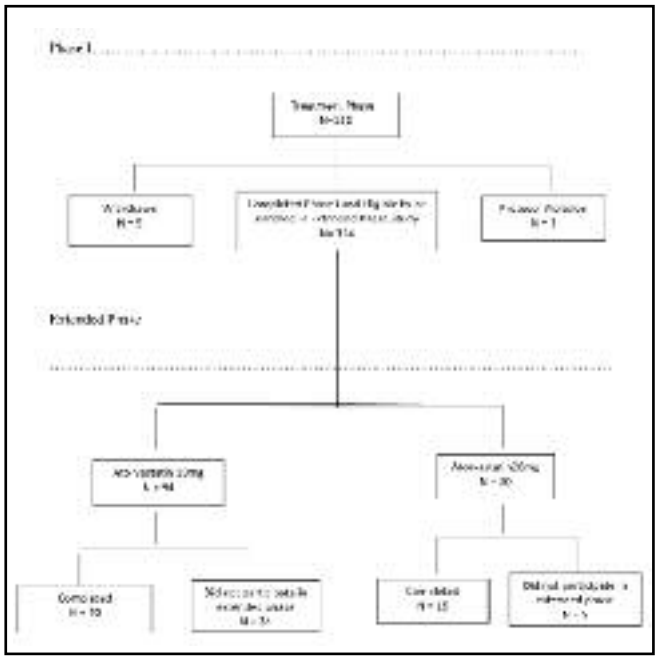

Fig. 1: Trial Profile

In the extended Study, eight patients withdrew from the study because of adverse event related to study medication or adverse event(s) perceived by patient to be because of study medication. This includes the 2 patients who had myalgia, one with lethargy and one patient with joint pain which got relieved after stopping the study drug. One patient withdrew because of pregnancy. One patient withdrew from the study due to hypopigmentation of the lower lip. Two patients had complained of weight gain and facial puffiness but these were not verified by the investigators.

Clinical chemistry examination at the final visit at 52 weeks revealed an ALT elevation in 4 patients with the maximum reading of 64 U/L, AST increase in one patient to 59 U/L, total bilirubin increase in 3 patients with the maximum reading of 29 umol/l and a CPK increase in 7 patients with 545 U/L as the maximum reading recorded. None are clinically significant elevations.

DISCUSSION

Management of patients with dyslipidemia involves a combination of dietary modification, exercise and drug therapy. Over the last 2 decades, statins have become an essential armamentarium in reducing the risk of CAD.

The National Institutes of Health has put emphasis on research that translates the benefits demonstrated in clinical research into effective treatments in non-research settings[9]. In an effort to show therapeutic efficacy, randomized controlled trials (RCT) in general impose certain constraints on eligibility, concomitant medication and end-points that might limit the generalisation of their conclusions. The main objective of an ideal clinical trial should be its relevance to the practicalities of everyday patient care and should be designed in such a way to ensure maximum generalisability to the real life settings unlike typical RCT[10].

Our study was designed to demonstrate the effectiveness of a generic atrovastatin (Storvas) in routine clinical setting. In the first phase of our open labeled study for a period of 8 weeks, the generic atorvastatin was shown to be effective and safe. The LDL-cholesterol lowering effect was maintained at one year. These results are comparable with the results reported in other studies[11, 12].

In trials, improved outcomes for trial participants are reported whether they are in the intervention or control arm because of a number of potential sources of trial effects[13] such as 'Hawthorne effect'[14], the care effect and the protocol effect[15]. The Hawthorne effect may result in improvement in outcome in trial due to factors which are not related to the effect of an intervention. Possible confounding factors include the effect of better supportive care and changes in behavior of subjects during the conduct of a clinical trial. We attempted to minimize the phenomenon by imposing few restrictions on the routine care of the participants by their physicians. The participants were followed up in the usual manner by their own practice physicians and they attended the trial clinic only at the end of the study for final blood sample collection. A retrospective data base analysis of long term course of LDL-C after initiation of statin in usual care setting found 28% mean LDL-C decrease from baseline at 18 months[16]. In this study, the mean percentage reduction of LDL cholesterol was 36.45%, 37.87% and 32.16% at week4, week 8 and week 52 respectively.

This study demonstrated that achievement of NCEP-recommended LDL-C targets is feasible with a generic atrovastatin monotherapy for the majority of patients with dyslipidemia. 82% of subjects achieved their LDL-targets at week 4 and 81% at week 8 and 69% maintained that target at week 52. The LDL-C target goal achievement with 10 and 20mg of Storvas also fares well compared to published data where it is reported that treatment with 10 mg of atorvastatin resulted in achievement of NCEP-recommended target LDL concentrations in 32% of patients; 53% of patients achieved target concentrations with 10 to 20 mg of atorvastatin and 79% reached targets with up to 80 mg of atorvastatin[17].

In our study the 'CHD or CHD risk equivalent group' was better at maintaining the target LDL-C over long term compared with the group with one or no risk factors. The observation which has also been reported in other studies[18] is likely due to poorer compliance to therapeutic life style changes in the group who perceive their risk of cardiovascular disease to be lower.

Atorvastatin has been shown to reduce hepatic secretion of very-low-density lipoproteins (VLDL), resulting in a reduction in plasma triglycerides as well as LDL-C,[19] and the ability to reduce triglycerides is considered to be a class effect related to the baseline triglyceride level and significant reductions occur only in patients with high baseline triglycerides[19].

Our study found a significant reduction in triglyceride levels even when the mean baseline triglyceride level was within normal range (1.60mmol/L) though just like other major primary and secondary prevention trials our study excluded

patients with highly elevated triglyceride levels (>5.65mmol/L). Literature comparing other statins reports no significant or dose dependent effect on triglyceride when baseline triglyceride was < 150mg/dL (<1.69mmol/l) [20].

The generic atorvastatin, Storvas, was well tolerated. The adverse events reported during the initial 8 weeks of therapy were consistent with the literature. Approximately 10% of patients treated with statins experience some form of muscle-related adverse events in clinical practice. These range from asymptomatic creatine kinase (CK) elevation, muscle pain and weakness to rhabdomyolysis and death [21]. 1.5–3.0 percent of patients taking a statin complain of muscle pain, weakness, or cramps. The numbers reported are said to be similar for patients receiving placebo [22, 23].

Although elevated levels of hepatic enzymes were of concern when statins were first introduced, a review of data from large clinical trials shows that elevations in hepatic enzymes are rare and do not lead to clinically significant liver disease [24]. During the first 8 weeks of Storvas study, the transaminases were slightly elevated in 2 patients and the maximum elevation was 1.4 times the upper limit of the normal range(ULN). During the subsequent 44 weeks, there were mild insignificant elevations of transaminases.

Although our study was not designed to capture all adverse effects in the medium term, we did not observe serious drug related adverse events during the first year of therapy.

In an overview of the clinical safety profile of atorvastatin, it is reported that 0.7% of patients had confirmed transaminase elevations greater than 3 times the upper limit of the normal range. Most elevations occurred within 16 weeks of beginning treatment. No patients had a conclusive characterization of drug-induced myopathy [25]. It is reported that small, clinically insignificant increases in transaminases and CK are commonly observed with all statins [26].

Though atorvastatin is generally found to be very effective in reducing the LDL-C, the cost of the drug precludes its use in many patients who are in need of it most. The cholesterol lowering profile of Storvas at a lower cost with no increased risk of adverse events will be beneficial and affordable for many economically underprivileged patient populations and reduce health expenditure. Considering the need for long term use of statins for both primary and secondary prevention of CHD, cost reduction would be beneficial to even affluent societies.

CONCLUSION

The generic atorvastatin, Storvas, is safe and effective for the long term the treatment of primary hypercholesterolaemia in the usual clinical care setting.

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