Utilization Pattern of Statins in an Indian Population

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Research Article

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Abstract

Atheroma is a focal disease which affects the intima of large as well as medium sized arteries. Numerous risk factors for atheromatous disease were recognized by epidemiological studies. Some of them cannot be altered (e.g. family history of ischemic heart disease. The main objective of the thesis was to evaluate the safety and efficacy of statins in an Indian population attending a cardiology clinic and thereby assess the utilization pattern of the drugs. It was a prospective study. The study was conducted in Department of Cardiology, Kovai Medical Center and Hospital in Coimbatore, Tamil Nadu. The study was conducted over a period of 6 months from July 2011 to December 2011. The data was collected from various sources such as patient's case reports, treatment charts and also through telephonic conversations with the patients. Patients who met the study criteria were included in the study. The study was explained to the patients and their oral consent was taken. Ethical committee approval was obtained from Kovai Medical Center and hospital. Parameters like age, sex, current medications, past medical and medical history were collected from treatment charts and patient's case reports. Patient's adherence to Statins was checked by using Morisky's 8 questionnaires through telephonic interview with the patients. Naranjo's causality assessment scale was used to assess the reported ADRs. In this prospective study, the utilization pattern of statins was evaluated in a total of 32 patients who were diagnosed with dyslipidemia for the first time and obtained there lipid profiles at least once during the study period. The LDL-C level of the patients was assessed at baseline and at review. In the study population the prevalence of dyslipidemia was high in males than in females. 93.75% of the patients were males and the remaining 6.25% of the patients were females. Most of the patients were at an age group of 61-70years.78.12% of the patients were using Atorvastatin and 21.88% of the patients were using Rosuvastatin. Among all the classes of Statin Atorvastatin 40mg was prescribed in most of the patients (28.12%). No patients were using Atorvastatin 20mg and Rosuvastatin 5mg. Atorvastatin 80mg was found to produce maximum lipid reduction among all the other classes of statins in the study population (37.62%) and the least by Atorvastatin 40mg. Atorvastatin showed a mean lipid reduction of 21.29%,24.16% at doses like 5mg and 10mg respectively. The main ADR found in the study population was muscle pain and was predominant in the age group of 61-70 years. The baseline LDL-C of the patients prescribed with Atorvastatin 10mg (145.25±21.96) was found to be higher than that of the patients with Atorvastatin 40mg (101.77±12.24).

Introduction

Atheroma is a focal disease which affects the intima of large as well as medium sized arteries. Numerous risk factors for atheromatous disease were recognized by epidemiological studies. Some of them cannot be altered (e.g. family history of ischemic heart disease. Dyslipidemia is one of the contributing factors for the cardiovascular disease which can be modified and are potential targets for therapeutic drugs (**1**).

LIPOPROTIEN TRANSPORT IN HUMAN BODY

Lipids and cholesterols are transferred in the blood as macromolecular complexes. This macromolecular complex is called lipoproteins. The central cores of these complexes have a hydrophobic lipid in a hydrophilic coat which is polar in nature. The lipoproteins are classified into four groups based on the fraction of the core lipids and the type of

apolipoprotiens. These four groups differ in their density and the size. (**1**)

The four types of lipoproteins are
- ❖ Low Density lipoprotein (HDL)
- ❖ High density lipoproteins(LDL)
- ❖ Very low density lipoproteins (VLDL)
- ❖ Chylomicrons

DYSLIPIDIMIA

Dyslipidemia is defined as the presence of abnormal amount of lipids in the blood. The risk for cardiovascular disease increases with increased LDL cholesterol concentrations and decreased HDL cholesterol concentrations. (**1**)

Statins are used for primary and secondary prevention of cardiovascular diseases. When it is used to treat dyslipidemia in patients without any history of cardiovascular disease or atherosclerotic vascular disease it termed as primary prevention and when used in patients with a history of Cardiovascular diseases or cardiovascular risk factors is said to be secondary prevention (**2**).

All statins act by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is accountable for the change of HMG-CoA to mevalonate. This results in a compensatory increase in the number of LDL receptors, primarily in the liver, an increase in LDL plasma clearance and a reduction in LDL production. Although the most pronounced effect of statins is the lowering of LDL-C levels, these agents also increase HDL-C and decrease total-C and plasma triglycerides (**3**).

Cardiovascular diseases are progressively rising as the major cause of death throughout the world. The implications of cardiovascular diseases are more significant in India. 3.75 million Deaths are reported due to cardiovascular diseases in 2010 across India. Out of this 2 million deaths were due to coronary artery diseases and heart attacks. The Lancet finds that in the next two years India will put up with 60% of the world's heart disease burden, additionally studies reviled that the average age of patients prone to heart disease is lower among Indian population than in the developed countries but are more likely to have various heart diseases (**4**).

National Commission on Macroeconomics and Health (NCMH), a government of India undertaking estimates that there will be around 62 million patients with CAD by 2015 in India. Out of this 23 million patients are expected to be at the age less than 40 years. The main cause of CAD is atherosclerosis of large and medium sized arteries and Dyslipidemia is considered as the primary cause (**5**).

More than 40% of individuals over 65 years seeks medical treatment and hospitalized for coronary diseases at least once in their lifetime. The quality of life of the patients will be adversely affected by the recurrent hospitalization and disability in these patients. The estimated prevalence of coronary artery disease in these patients are more than 40% and is associated with high risk of mortality (**6**).

Although the treatment of dyslipidemia for the prevention of cardiovascular diseases is common, all the patients who are treated with statins are not getting the benefits. Noncompliance and discontinuation of the therapy results in failure of the treatment. The risk of non compliance of the statin therapy varies from 15%-30% within the first year when the therapy is initiated (**7**).

Rhabdomyolysis is the major ADR caused by statins, but the incidence is very rare since it is well tolerated in patients. The incidence of rhabdomyolysis apart from the use of statins is only 50%. Diffuse myalgias and weakness over several days will present in case of statin induced rhabdomyolysis, the presentation of the symptoms varies in Patients.

The symptoms of rhabdomyolysis may be atypical so strict monitoring of the patients is needed patients having elevated creatine kinase level. Patients with rhabdomyolysis show symptoms like common muscle pain and fatigue. The average time for developing statin induced rhabdomyolysis is approximately 1 year (**8**).

Statins are highly effective for the secondary prevention of CAD and are well tolerated in patients. Hence they are the mainstay for CAD patients. Drug utilization evaluation study the important factors related to prescribing, dispensing, administering and usage of medication, and its associated events. The study is also aimed to note the adverse drug reactions reported and to relate them to the different characteristics of the study population. From the information on adverse drug reactions, changes can be made and drug use improved. This can prevent unnecessary withdrawal of the medication by the patient himself.

There is not much information available regarding the utilization pattern of statins in the Asian population, hence the study was undertaken to determine the utilization pattern of statin in an Indian clinical setting.

Material and Method

The main objective of the thesis was to evaluate the safety and efficacy of statins in an Indian population attending a cardiology clinic and thereby assess the utilization pattern of the drugs. It was a prospective study. The study was conducted in Department of Cardiology, Kovai Medical Center and Hospital in Coimbatore, Tamil Nadu. The study was conducted over a period of 6 months from July 2011 to December 2011. The data was collected from various sources such as patient's case reports, treatment charts and also through telephonic conversations with the patients. Patients who met the study criteria were included in the study. The study was explained to the patients and their oral consent was taken. Ethical

committee approval was obtained from Kovai Medical Center and hospital. Parameters like age, sex, current medications, past medical and medical history were collected from treatment charts and patient's case reports. Patient's adherence to Statins was checked by using Morisky's 8 questionnaires through telephonic interview with the patients. Naranjo's causality assessment scale was used to assess the reported ADRs.

Inclusion criteria

All patients diagnosed with dyslipidemia and cardiovascular risk factors, prescribed with statins for the first time in Department of Cardiology, Kovai Medical Center Hospital Coimbatore, Tamil Nadu, India. The Institutional Review Board approved the research work to be conducted in KMCH.

Exclusion criteria

a) Patients who were previously on Statin therapy will be excluded from the study.

b) Patients without a lipid profile at their first review.

Statistical Analysis

Individual variables have been expressed as percentages or Mean ± SE. The reduction LDL-C level from the baseline at review was compared using paired student 't' test. p value of ≤0.05 was taken as significant.

Results

In this prospective study, the utilization pattern of statins was evaluated in a total of 32 patients who were diagnosed with dyslipidemia for the first time and obtained there lipid profiles at least once during the study period. The LDL-C level of the patients was assessed at baseline and at review. In the study population the prevalence of dyslipidemia was high in males than in females. 93.75% of the patients were males and the remaining 6.25% of the patients were females. Most of the patients were at an age group of 61-70years.78.12% of the patients were using Atorvastatin and 21.88% of the patients were using Rosuvastatin.

Among all the classes of Statin Atorvastatin 40mg was prescribed in most of the patients (28.12%). No patients were using Atorvastatin 20mg and Rosuvastatin 5mg. Atorvastatin 80mg was found to produce maximum lipid reduction among all the other classes of statins in the study population (37.62%) and the least by Atorvastatin 40mg. Atorvastatin showed a mean lipid reduction of 21.29%,24.16% at doses like 5mg and 10mg respectively. Rosuvastatin 10mg showed 32.574% LDL-C reduction at review. Statin use were assessed in terms of type of prevention and found that 59.37% of patients were prescribed for secondary prevention and the remaining 40.62% of patients were on treatment with statins for primary prevention of cardiovascular diseases. Patient's adherence to statin therapy was checked by using Morisky's

8 questionnaires. 67.4 % of patients were highly adherent to their treatment plan. 22.58% of patients showed medium adherence and 9.67% of patients showed low adherence to their treatment plans. Statins are well tolerated in most of the patients. Muscle pain was the only Adverse Drug Reaction found in the study population.74.2% of the patients was free from muscle pain and 25.8% patients complained about muscle pain.

The adverse drug reactions and patient's age were related in the study population. 87.5% of the patients who developed muscle pain were at an age group of 61-70 years and 12.5% of patients were at an age group of 21-30 years. The prevalence of ADR was found to be more in geriatric population. The mean age of the patients using Atorvastatin and Rosuvastatin was 53±2.59 years and 43.714±3.25 years respectively. 68% of the patients were using Atorvastatin for secondary prevention and 32% for primary prevention.

Table 1: Demographic Characteristics of the Patients Using Statins

Demographic characteristics	Atorvastatin n(%)	Rosuvastatin n(%)
Gender		
Male	23(71.8)	7(21.87)
Female	2(6.25)	0
Age(mean ±standard Error, year)	53±2.59	43.714±3.25
Indication for cardiovascular prevention		
Primary	8(32)	5(71.42)
Secondary	17(68)	2(28.57)

Table 2: Percentage Lipid Reduction at Different Doses of Prescribed Statins

PRESCRIBED DOSES OF STATIN	PERCENTAGE LIPID REDUCTION
ATORVASTATIN5mg	21.29%
ATORVASTATIN10mg	24.16%
ATORVASTATIN40mg	17.83%
ATORVASTATIN80mg	37.628%
ROSUVASTATIN10mg	32.574%

TABLE 3: LDL-C Reduction at First Review

Drug	Baseline LDL-C Level(mean ± SE)	LDL-C at Review (mean ±SE)	LDL-C Reduction (mean ± SE)	p value
Atorvastatin 5mg	77.33±16.20	74±6.65	3.3±9.9	<0.7
Atorvastatin 10mg	145.25±21.96	113.5±16.18	31.75±9.8	<0.02
Atorvastatin 40mg	101.77±12.24	66.11±7.49	33.25±9.714	<0.01
Atorvastatin 80mg	119.4±12.07	74.8±11.33	44.6±10.74	<0.02
Rosuvastatin 10mg	120.16±21.07	74.8±11.44	28.33±12.95	<0.1

71.42% of the patients were prescribed with Rosuvastatin for primary prevention and the remaining 28.57% for secondary prevention. In all the patients

using Atorvastatin, 68% of patient's target LDL-C level was <100mg/dl. 12% and 20% patient's target LDL-C level were <130mg/dl and <160mg/dl respectively. Similarly in case of patients who were on treatment with Rosuvastatin the LDL-C goal was <100mg/dl for 28.57% of patients and < 130mg/dl and <160mg/dl for 42.85% and 28.57% respectively. The outcomes of the therapy were illustrated in Table 3. Out of the total 25 patients prescribed with Atorvastatin, 24 patients attained their target LDL-C level at first review. 7 patients were using Rosuvastatin and 6 patients were able to achieve their target LDL-C level. The mean baseline of the patients using Atorvastatin 5mg, 10mg, 40mg and 80 mg were 77.33±16.20mg/dl, 145.25±21.96mg/dl, 101.77±12.24mg/dl, and 119.4±12.07mg/dl respectively. The mean baseline of the patients using Rosuvastatin 10mg was found to be 120.16±21.07md/dl. The LDL-C levels of the patients were assessed at baseline and at first review. The mean reduction in LDL-C level at different doses of the Statins is expressed as mean ± SE. The mean lipid reduction for Atorvastatin 5mg, 10mg, 40mg and 80mg was found to be 3.3±9.9, 31.75±9.8, 33.25±9.714, 44.6±10.74 respectively and for Rosuvastatin 10mg was 28.33±12.95. The relationship between the LDL-C level of the patients at baseline and at the review was estimated by using student t test at each dose of Statins.

The results revealed that there was a significant reduction in LDL-C level from the baseline at review in patients using Atorvastatin 10mg (p<0.02), 40mg (p<0.01) and 80mg (<0.02).There was also a considerable reduction in the LDL-C level even though the reduction was found to be insignificant in patients on treatment with Atorvastatin 5mg and Rosuvastatin 10mg. Causality assessment of the reported adverse drug reactions are carried out by using Naranjo's causality assessment scale. Muscle pain was only the ADR reported by the patients using Atorvastatin 40mg and 80mg and it was found as a possible reaction of the drug.

Discussion

In a study conducted in Warangal district of Andhra Pradesh with 1496 adults and older individuals dyslipidemia was found in 52.7% were males and 42.9% were females. The incidence dyslipidemia was predominant in all age groups, but in middle age group (40– 59 years) this increase was found to be highly significant. (9). The patients prescribed with statins for dyslipidemia were at younger age group when compared to the non users of statins and males are more in this category (10). In our study population also the prevalence of dyslipidemia was high in males than in females. 93.75% of the patients were males and the remaining 6.25% of the patients were females.

The frequency of cardiovascular events increases sharply with the increase in age. The incidence of CV disease and associated risk factors are considerably higher in older individuals. Cardiovascular disease is the most important reason for death in older patients, out of this over 80% of deaths are reported due to coronary heart disease (CHD) or stroke occur in individuals 65 years of age or older. So the prevention and recurrent of CV events in older individuals remains a major dispute. (11). However in our study we found that maximum number of patients was diagnosed with dyslipidemia at an age group of 61-70years.

2479 patients with dyslipidemia were included in a study conducted in Thailand. All the patients were first time users of statins and almost 90% of the subjects included in the study were prescribed with Simvastatin. Atorvastatin and Pravastatin were used by only 8% and 2% patients respectively. It was found that about 58.0% of the patients were on statin therapy for primary prevention (12). In our study population 78.12% of the patients were using Atorvastatin and 21.88% of the patients were using Rosuvastatin. Among all the classes of Statin Atorvastatin 40mg was prescribed in most of the patients (28.12%). No patients were using Atorvastatin 20mg and Rosuvastatin 5mg.

It was found that about 58.0% of the patients were on statin therapy for primary prevention in a retrospective analysis done in Thailand (13). In our study we assessed the statin use in terms of type of prevention and found that 59.37% of patients were prescribed for secondary prevention and the remaining 40.62% of patients were on treatment with statins for primary prevention of cardiovascular diseases.

The mean lipid reduction by Atorvastatin at doses of 5mg, 10mg, 20mg, 40mg and 80mg was 45%, 37%,, 43%, 50% and 53% respectively. (14). In our study population Atorvastatin 80mg was found to produce maximum lipid reduction among all the other classes of statins in the study population (37.62%) and the least by Atorvastatin 40mg. Atorvastatin showed a mean lipid reduction of 21.29%,24.16% at doses like 5mg and 10mg respectively. Rosuvastatin 10mg showed 32.574% LDL-C reduction at review.

In a study conducted in a health maintenance organization setting it was found that persons aged below 50 years were at high risk of poor adherence to statin therapy and the assessment proposed that the relationship between age and gender may be reasonably steady after three years of therapy with Statins. (15). Morisky's 8 questionnaire was used in our study to check the Patient's adherence to statin therapy was checked by using 67.4 % of patients were highly adherent to their treatment plan. 22.58% of patients showed medium adherence and 9.67% of patients showed low adherence to their treatment plans.

About fourteen clinical trials were conducted in 34,272 participants, out of which in 11trials   take on patients with specific conditions like raised lipids, diabetes, hypertension it was found that mortality was decreased by the use of statins where the endpoint was both fatal and non fatal CVD. There was no muscle pain and associated adverse drug reactions were not detected on treatment with statins. (**7**). Recent investigations reveal that age, race, work outs, and perioperative conditions may contribute to statin induced muscle toxicity. (**5**).The finding of our study was also the same .Statins is well tolerated in most of the patients. Muscle pain was the only Adverse Drug Reaction found in the study population.74.2% of the patients was free from muscle pain and 25.8% patients complained about muscle pain. The adverse drug reactions and patient's age were related in the study population. 87.5% of the patients who developed muscle pain were at an age group of 61-70 years and only 12.5% of patients were at an age group of 21-30 years. The prevalence of ADR was found to be more in geriatric population.

The mean age of the patients using Atorvastatin was 59.8±0.8, and 70.6% of the patients were using Atorvastatin for primary prevention and 29.4% of the patients were using it for secondary prevention in a study carried out in Thailand (**19**). But in our study the mean age of the patients using Atorvastatin was 53±2.59 years. 68% of the patients were using Atorvastatin for secondary prevention and 32% for primary prevention.

About 6814 persons at an age group of 45 to 84 years without any CVD problems in the year 2000 to 2002 in a multicenter cohort study. Models were established to adjust the variables by using Poisson regression. 30% of the patients were diagnosed with dyslipidemia, 54.0% patients reported the use of statin therapy and the target was achieved in 75.2% of patients. (**18**). In our study population, Out of the total 25 patients prescribed with Atorvastatin, 24 (96%) patients attained their target LDL-C level at first review. 7 patients were using Rosuvastatin and 6 patients were able to achieve their target LDL-C level.

Conclusion

The aim of the study was to assess the Statin use in an Indian clinical setting in terms of class, dose, and type of prevention and monitoring of Adverse Drug Reactions. In the study population Atorvastatin was prescribed in 78.12% of patients and Rosuvastatin was prescribed in 28.87% of the patients only. Most of the patients are prescribed with Atorvastatin 40mg (28.12%) and the least number of patients were prescribed with Rosuvastatin 20mg (3.12%).

The lipid reduction properties of Statins were assessed by measuring the LDL-C level of the patients at baseline and at review. The study revealed that at review, Atorvastatin showed a significant reduction in LDL-C level from the baseline at prescribed doses 10mg, 40mg, and 80mg. There was a substantial reduction in the LDL-C level from the baseline in the patients prescribed with Atorvastatin 5mg and Rosuvastatin 10mg at review, eventhough the reduction was found to be non significant.

The study was also aimed to check the efficacy of statin to achieve the target LDL-C level of the patients and it was found that 93.75% of the patients achieved their target LDL-C level on treatment with statins.

The Adverse Drug Reactions are monitored and related it to different characteristics of the study population. The main ADR found in the study population was muscle pain and was predominant in the age group of 61-70 years. The baseline LDL-C of the patients prescribed with Atorvastatin 10mg (145.25±21.96) was found to be higher than that of the patients with Atorvastatin 40mg (101.77±12.24).

Patient's adherence to Prescribed Statin was checked by using Morisky's-8 questionnaire. Patient's adherence to statin therapy was checked by using Morisky's 8 questionnaires. 67.4 % of patients were highly adherent to their treatment plan. 22.58% of patients showed medium adherence and 9.67% of patients showed low adherence to their treatment plans.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests