World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Therapeutic Approach to Reduce Cardiovascular Risk by Modulating Immune Function and Inflammatory Process

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Received: 15-09-2016 / Revised: 03-10-2016 / Accepted: 21-10-2016 / Published: 31-10-2016

ABSTRACT

The aim of this study is to prevent the severity of psoriasis disease and cardiovascular risk by modulating the immune function and inhibiting the inflammatory process by a novel drug Atorvastatin. Inflammation is a primary factor affecting many autoimmune diseases. Epidemiological studies showed that immuno-inflammatory diseases like psoriasis are associated with a greater morbidity and mortality due to cardiovascular risk. It is an interventional experimental study, divided in two phases. One phase was preclinical study conducted on adult Wistar Albino rats and the other phase was clinical study on psoriatic patients of chronic plaque type. The efficacy and safety profile of drug was measured preclinically by morphological study of rat's myocardium thus clinically it measured by PASI, DLQI, CRP, LFTs and Lipid profile of psoriatic patients. Results of this study revealed that in psoriatic patients the immune mediated inflammation with cardiovascular events was prevented by Atorvastatin. Therefore an additional benefit is achieved in psoriatic patients. Firstly it modulates the immune function and inhibits inflammatory process, secondly it protects them against cardiovascular risk.

Key Words: Doxorubicin; Atorvastatin; Cardio vascular risk; Psoriasis.

INTRODUCTION

Immuno-inflammatory diseases or autoimmune diseases are caused by 150 genetic conditions and majority of them life lasting. These diseases are mostly detected late in life, when the patient experiences an organ damage [1]. The autoimmune diseases and atherosclerosis have many similarities. There are many common pathogenic pathways of inflammation that are parallel to each other [2]. Such as rheumatoid arthritis shows an activation of macrophages, endothelium and TH1 and TH2 helper T-cell ratio imbalance [3, 4]. In systemic lupus erythematosus the auto- antibodies, TNFα and IL10 induce vascular injuries and thrombosis [5]. Psoriasis is chronic, recurrent immune mediated inflammatory disease with genetic predisposition. The purpose of this study is to reduced severity of a disease and inhibit cardiovascular risk by hampering the immuno inflammatory process of psoriasis by Atorvastatin. The hallmark of psoriasis and cardiovascular risk is an immune mediated inflammatory process. There are many theories that prove that both are related to each other .One theory states that both are initiated by T-lymphocytes such as Th1 and Th17. The activation of inflammatory cells, chemokines, cytokines and the growth factors have a key role in pathogenesis of psoriatic plaque and atherosclerosis [6, 7].

Doxorubicin is an anthracycline antibiotic, used as an anticancer drug. The cytotoxic effect of doxorubicin is produced by inhibition of an enzyme Topoisomerase II (DNA gyrase), which blocks the synthesis of RNA and DNA by generation of a free

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radical [8]. Another strong association between oxidative stress and inflammation is cytokines release [9, 10]. The most important pro-inflammatory cytokine is released after doxorubicin induced toxicity is tumor necrosis factor α (TNFα) which produces cardiac damage [11].

Atorvastatin is a well-known, economic, antihyperlipidemic drug and has an anti-inflammatory as well as immuno-modulatory effect [12]. Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalysis the cholesterol synthesis [13]. Mevalonate is the precursor not only of cholesterol but also of many nonsteroidal-isoprenoid compounds. Statin blocks synthesis of geranylated proteins which are responsible for the proliferation and migration of smooth muscle cells which causes growth of atherosclerotic and psoriatic plaque. Atorvastatin suppresses intercellular adhesion molecules (ICAM-1), leukocyte function associated-1 (LFA-1), and C-reactive protein (CRP) level. It also inhibits expression of major histocompatibility complex (MHC) class II molecules on macrophages, endothelial cells and smooth muscle cells. Nitric oxide generation is another important function of Atorvastatin involved in psoriasis and cardiovascular risk. Dose of Atorvastatin is 10-80 mg/dl while its half-life is 14 hrs [14]. Adverse events are rare and include myopathy and abnormal liver enzymes [15].

MATERAL AND METHODS

Preclinical Study: Ninety laboratory breed adult Albino Wistar rats (30 in each treatment groups) were divided equally into three groups. Group A (Control), Group B (Doxorubicin toxicity), Group C (Atorvastatin + Doxorubicin). All animals weighing between 150-200 mg were taken in this experimental innovative study, approved by ethical committee of Jinnah Post Graduate Medical Center, Karachi. The animals were kept at room temperature and lighting was maintained. Standard laboratory animal feed was provided and supplemented with a free access of water. During assigned times of the experiment, rats from each group were anesthetized and sacrificed 1 week after the last dose of the injection. The thoracic cavity was rapidly opened, exposing the beating heart, which was then excised, washed with physiological saline and processed for histological study by light microscopy. Billingham scale for grading anthracycline induced cardiotoxicity used to assess the biopsy slides as explained by Berry et al. (1998) [16].

Clinical Study: In this interventional study out of the selected 75 psoriatic patients, 70 patients were able to complete the study. Patients were prescribed Atorvastatin 80 mg for first three months followed by 40 mg for next three months. The total duration of this study was 180 days with six follow up visits including both male and female ranging between the age of 25-65 years having PASI scoring of >7 up to 12 with a CRP of ≥3.Those patients who had recent statin and steroid therapy in the previous one month and a history of any other illness or pregnancy and lactation were not included in this study group.

The efficacy of drug was assessed by Psoriasis Area and Severity Index (PASI).The current gold standard for assessment of extensive psoriasis is the Psoriasis Area and Severity Index (PASI). Fredriksson and Pettersson created PASI in1978 as a method to evaluate the clinical efficacy of a new treatment for psoriasis. The highest potential known score is 75 and the lowest is 0 [17]. A PASI >12 defines severe, PASI 7–12 moderate, and PASI <7 mild psoriasis [18, 19]. PASI improvement explained by Rodgers et al. (2011) [20] are 50%, 75% and 90 %. FDA approved that 50% improvement in PASI would mean the treatment is efficient clinically [21].

C-reactive protein triggers inflammation that increases in psoriasis [22]. CRP is used for global index of disease severity .Monitoring CRP level can serve as an important prognostic factor while assessing response to treatment [23]. Elevated levels of CRP may be an independent risk factor for CVD in patients with psoriasis. The plasma levels of CRP in most healthy subjects is usually 1 mg/L [24].

Quality of life was evaluated by dermatological life quality index which was assessed on the first day of enrollment and finally reassessed after the therapy. Dermatological life quality index is a useful index for clinical grading of patients. It is used in accordance to instructions given by Finlay and Khan (1994) [25].

Psoriasis is associated with dyslipidemia, a risk factor for cardiovascular diseases. Atorvastatin decreases the S-Triglyceride, S-LDL, Cholesterol and increases S- HDL [26].

Safety profile of Atorvastatin measured by Liver function test and Creatine phosphokinase level. LFTs performed to analyze liver enzymes which are essential in the monitoring liver diseases. CPK is increased in muscle damage as Atorvastatin induces myopathy and liver damage [27, 28].

Statistical Analysis: Data was analyzed using SPSS version 21 (IBM). Initially, the data was entered on SPSS. Descriptive statistics were performed. Categorical variables were presented as frequency (percentages) and quantitative variables were presented as Mean ± SD. Initially, the pre-clinical results were analyzed. The variables were compared among the groups using the chi- square. The mean scores were compared using One Way ANOVA with post-hoc comparison. Subsequently the clinical data of Psoriatic patients was analyzed. The demographic characteristics were presented as frequency (percentages) and quantitative variables were presented as Mean ± SD. The lipid profile, Liver Function Test (LFT), Creatine Phosphokinase, Psoriasis Area and Severity Index (PASI), C - reactive protein (CRP) and Dermatological Life Quality Index (DLQI) were compared at the baseline, three months follow-up and six months follow-up by using the Repeated Measure ANOVA. The percentage change of PASI, CRP and DLQI were compared at three months and six months by using t –Test. Finally, the adverse events were reported as percentages. For all sets of analysis p-value < 0.05 was considered significant.

RESULTS

In preclinical study four rats of DOX- Group, three rats of Atorvastatin pre-treated and Control Groups died during the observational period. The general appearance of rats in Doxorubicin- Group's revealed the development of a pink tinge and red discharge from eyes and nose, abdominal enlargement and a gross weight loss. Decreased consumption of food and water was noticed as compared to the control and Atorvastatin pretreated group. Table 1 illustrates the comparison of three Groups after four weeks of treatment followed by microscopic study of myocardium.

Control Group showed myocardium arranged in regular striations with centrally placed nucleus, no degeneration or necrosis was observed and the myocardium had a normal size and acidophilic cytoplasm. In doxorubicin group the histopathological changes of rat′s heart tissue revealed altered architecture of cardiac muscle with focal morphological changes. In Atorvastatin pretreated Group all changes of Doxorubicin toxicity were prevented.

Table 2 illustrates Billingham scale for grading of anthracycline induced cardiotoxicity, as Grade 0 means no evidence of anthracycline toxicity, 0.5 means not completely normal but no evidence of anthracycline damage, Grade 1 means early myofibrillar loss, damage to 5% of all cells, Grade 1.5 means similar to Grade 1 but damage to 6% to 15% of all cells. Grade 2 means Clusters of myofibrillar loss and/or vacuolization, with the damage to 16%-25% of all cells. Grade 2.5 means Clusters of myocytes affected by myofibrillar loss and/or vacuolization with the damage to 16%-25% of all cells and Grade 3 means severe diffuse myocyte damage (> 35% of all cells). In this study the myocardial biopsy of control and Atorvastatin pre-treated Group occupied Grade 0.5 and doxorubicin Group expressed grade 2.

These histopathological changes of myocardium (vacuolization, infiltrate, loss of myofibrils, pyknosis, interstitial oedema and congestion of vessels) in all three Groups were illustrates in Figure 1, Figure 2 and Figure 3. On post hoc analysis highly significant difference were found between Group A (control) and Group C (preventive) with Group B (toxic) and no significant difference was found between Group A (control) and Group C (preventive).

In clinical study the demographic data of Table 3 and Figure 4 illustrates that most of the patients were smokers, positive family history of psoriasis, disturbed sleep and moderate PASI score. Table 4 illustrates that Atorvastatin showed highly significant change in outcome variables (PASI, DLQI and CRP). Atorvastatin have significant effects on lipid profile of psoriatic patients. Safety profile of different doses of Atorvastatin at different intervals as it illustrates in Table 5. Patients complained mostly nausea while none of the patients complained of myopathy or other adverse events even in higher doses of Atorvastatin as illustrated in Figure 5.

TABLE 1: ***Comparison of Biopsy Variables among Three Groups***

	Control *(Group A)* **(27)**	**Doxorubicin** *(Group B)* **(26)**	**Atorvastatin & Doxorubicin** *(Group C)* **(27)**	**P-value**
Cytoplasmic Vacuole				
No	**27 (100)**	**8 (30.77)**	**24 (88.9)**	
Yes	**0 (0)**	**18 (69.23)**	**3 (11.1)**	**0.001**
Interstitial Oedema				
No	**25 (92.6)**	**7 (29.6)**	**23 (85.2)**	
Yes	**2 (7.4)**	**19 (73.1)**	**4 (14.8)**	**0.001**
Hemorrhage				
No	**22 (81.5)**	**7 (29.6)**	**21 (77.8)**	
Yes	**5 (18.5)**	**19 (73.1)**	**6 (22.2)**	**0.001**
Fragmentation of Cardiomyofibrils				
No	**27 (100)**	**23 (88.5)**	**27 (100)**	
Yes	**0 (100)**	**3 (11.5)**	**0 (0)**	**0.039**
Hyalinization				
No	**27 (100)**	**23 (88.5)**	**27 (100)**	
Yes	**0 (0)**	**3 (11.5)**	**0 (0)**	**0.039**
Necrosis				
No	**27 (100)**	**25 (96.2)**	**27 (100)**	
Yes	**0 (0)**	**1 (3.8)**	**0 (0)**	**0.349**
Inflammatory Infiltrate				
No	**27 (100)**	**14 (53.8)**	**27 (100)**	
Yes	**0 (0)**	**12 (46.2)**	**0 (0)**	**0.001**
Pyknosis				
No	**27 (100)**	**25 (96.2)**	**27 (100)**	
Yes	**0 (0)**	**1 (3.8)**	**0 (0)**	**0.349**
Loss of Myofibrils				
No	**27 (100)**	**13 (50)**	**27 (100)**	
Yes	**0 (0)**	**13 (50)**	**0 (0)**	**0.001**

TABLE 2: ***Comparison of Mean of BILLINGHAM SCALE GRADE among Treatment Groups***

Group A (n = 27) Mean ± SD	**Group B (n = 26) Mean ± SD**	**Group C (n = 27) Mean ± SD**	**P-value**
0. 11 ± 0.21	1.94 ± 0.22	0.20 ± 0.32	0.0001

Histopathological Changes in Three Groups

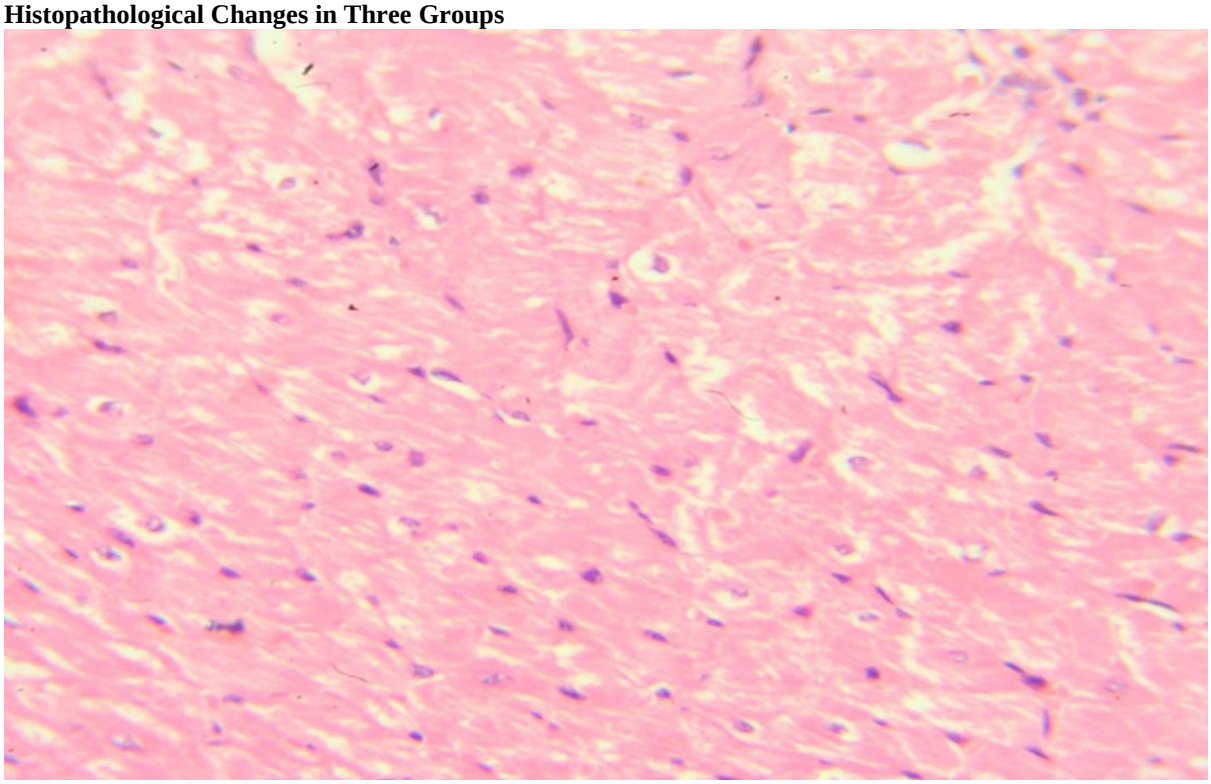


FIGURE 1

Doxorubicin Induced Cardiotoxicity (Group-B): Cytoplasmic vacuoles, interstitial Oedema and inflammatory infiltration between irregular wavy cardiomyocytes (H and E x 40)

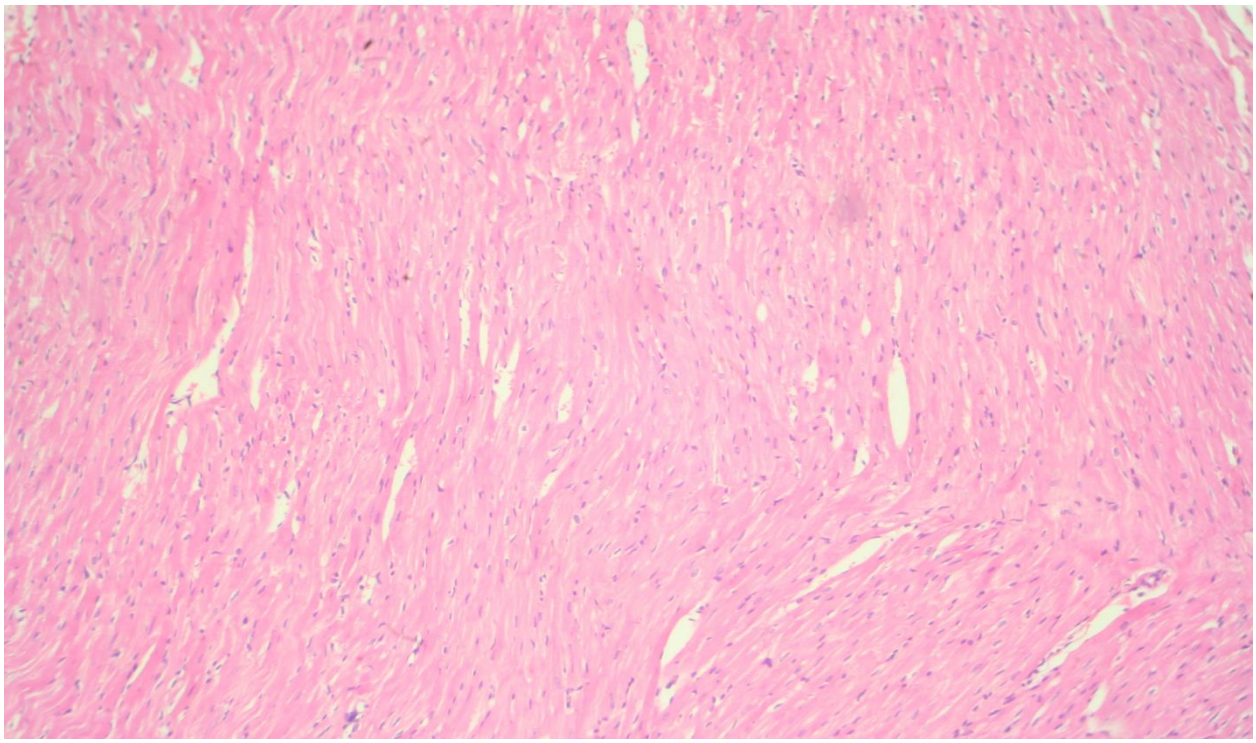


FIGURE 2

Control (Group-A): Normal architecture of myofibrils (H and E× 40)

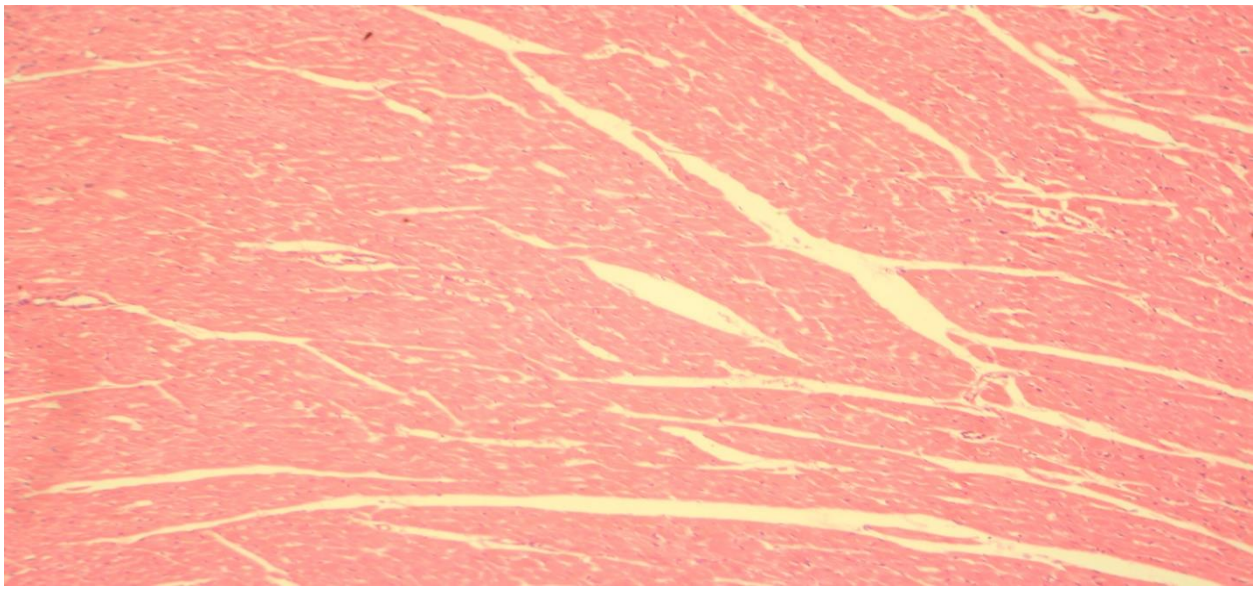


FIGURE 3
Atorvastatin Pretreated (Group-C):
Normal architecture of myofibrils with mild oedema (H and E: x 10.)

TABLE 3: ***Demographic Characteristics of Patients***

VARIEBELS	GROUP A
Age (Years)	47.89 ± 8.23
Gender	
Male	54 (77.15)
Female	16 (22.86)
Family History	37 (52.85)
History of Smoking	44 (62.86)
Sleep Disturbed	70 (100)
Duration of Disease	5.09 ± 2.18
Mild-PASI < 7	3 (4.28)
Moderate PASI (7-12)	67 (95.72)

FIGURE 4: ***Location of Lesion***

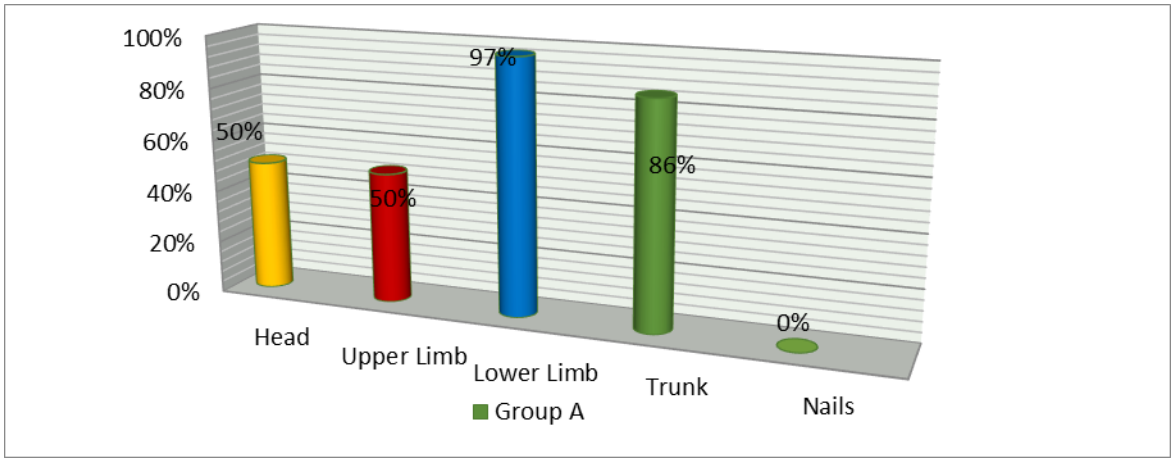


TABLE 4: ***Comparison of Outcome Variables (Psoriasis Area and Severity Index, C reactive protein & Dermatological Life Quality Index) among Patients at the Baseline and follow-ups***

Outcome Variables	Baseline	Three Months Follow-up	Six Months Follow-up	P-value
Psoriasis Area and Severity Index (PASI) (Percentage Change)	10.892 ± 1.19	3.821 ±0.448 (64.918±1.509)	2.718 ± 0.315 (75.073±.369)	0.0001
CRP (Percentage Change)	3.96 ± 0.55	3.26 ± 0.53 (17.617±4.93)	2.57 ± 0.58 (35.156±8.78)	0.001
Dermatological Quality Of Life (DLQI) (Percentage Change)	19.6 ± 1.98	-	5.63 ± 0.52 (71.053±3.464)	0.001

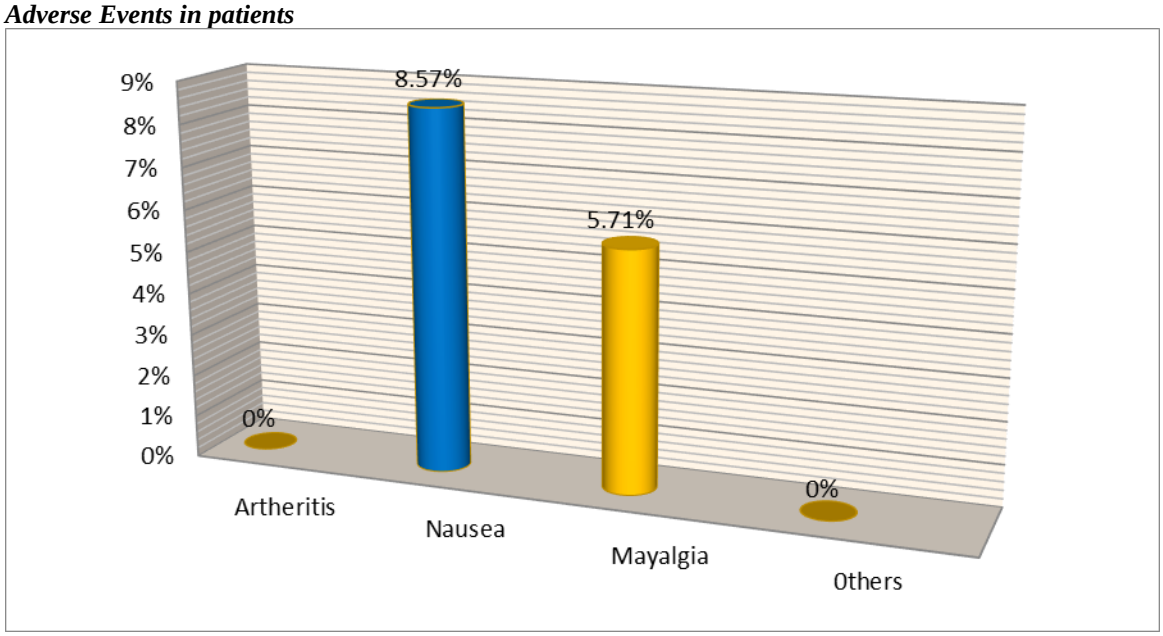
TABLE 5

Comparison of Biochemical Parameters in Patients at the Baseline and Follow-ups

VARIABELS	Baseline	Third Months Follow-up	Six Months Follow-up	P-value
Total Cholesterol (mg/dl)	193.73 ± 4.98	174.30 ±4.92	139.16 ± 5.10	0.001
Triglyceride (mg/dl)	145.71 ± 2.81	138.62 ±2.88	119.61 ± 3.19	0.001
High Density Lipid (mg/dl)	38.16 ± 1.33	39.30 ± 1.21	42.37 ± 0.98	0.001
Low Density Lipid (mg/dl)	140.90 ± 5.00	130.19 ±4.24	107.83 ± 4.88	0.001
Alanine Aminotransferase (U/L)	34.900±5.432	35.085 ± 5.383	35.228 ± 5.351	0.264
Aspartate Aminotransferase (U/L)	35.457±3.317	35.614 ±3.195	35.600 ±3.793	0.494
Gamma Glutamyl Transferase (U/L)	37.514±3.802	37.600± 4.318	37.885± 4.428	0.227
Alkaline Phosphatase	94.014±12.492	94.085 ±12.639	94.144± 12.863	0.950
Total Billirubin (U/L)	0.577± 0.121	0.595 ±0.144	0.602± 0.163	0.274
Creatine Phosphokinase (U/L)	82.814±14.505	83.042±14.272	82.128 ±17.139	0.151

FIGURE 5

Adverse Events in patients



DISCUSSION

Atorvastatin having remarkable effects on psoriasis and it is associated with cardiovascular risk. It has multiple responses on psoriatic patients. It reduced the severity of disease and modulates dyslipidemia with hsCRP. Therefore Atorvastatin decreased cardiovascular events by pleiotropic effects to amend immune system and thus hampering the inflammation. Preclinical study showed, significant results that supported the clinical study. Chronic inflammation leads to atherosclerosis which causes cardiovascular risks. Psoriasis is associated with cardiovascular events under the influence of inflammation, its association was broken by a single drug therapy with Atorvastatin.

Doxorubicin is the anticancer drug but due to its cardiac toxicity its use is limited in oncology. In this study Group B (Doxorubicin induced cardiotoxicity) reported the mean of Grade 2 toxicity, which was assessed by seven-point Billingham scale of biopsy [16]. The morphological changes in myocardium includes vacuolar degenerations, vascular dilatation/ congestion, marked oedema and inflammatory cells infiltrate with focal loss of myofibrils, pyknosis, necrosis and fibrosis [29]. All variables of seven–point scale of biopsy were prevented in Group C (Atorvastatin pretreated-group). A significant difference was found between Group A (control) and Group B (cardiotoxic) but there were no significant changes between Group A and Group C (Atorvastatin pretreated) on histopathological study of rat's myocardium [30].

Psoriasis induces an immune mediated inflammation which leads to cardiovascular events and dyslipidemia. The key factors of psoriasis and cardiovascular events are Th1 and Th17, over an expression of MHC-II and LFA-1, the release of cytokines such as TNFα, IL6, IL1, and CRP which is a strong biomarker and predictor of cardiovascular risk. Dyslipidemia itself acts as one of the major risk factors of cardiovascular events [31, 32]. All these factors induce a pathological change in cardiomyocytes, day by day in the same mode as Doxorubicin induced cardiotoxicity which is time dependent from vacuolization to loss of myofibrils. It is not possible to take patients heart biopsy so this phase was performed on rats.[29] The changes noticed in general appearance in Doxorubicin- Group B rats developed a pink tinge and red discharge from eyes and nose, abdominal enlargement, gross weight loss and lethargic. The fur became messy. They showed a decreased in food and water consumption as compared to the control and Atorvastatin pretreated Group [33, 34].

During a clinical study the demographic data of psoriatic patients were heavy smokers that showed disturbed sleep [35]. Psoriasis Area and Severity Index (PASI), is used to measure the progress of disease after and before the treatment. By using this index a researcher can easily explain the efficacy of drug. The most common sites were elbows, knees, scalp, umbilicus and lumbar area [36]. In this study 69 patients revealed PASI- 50 and one patient was reported with PASI-75 at the end of the six months. One study reported that 40 mg Atorvastatin improved PASI change upto 75% but their sample size was small. However in our study the PASI change in patients showed that the drug was effective and safe [37].

The base line hsCRP was 3.96 ± 0.55 in this study. As CRP is the marker of inflammation and cardiovascular risk [38]. It is the excellent predictive marker for psoriasis disease severity before and after the treatment [23]. The mean percentage changed from the base line to six months were 35.16 ± 8.79 in psoriatic patients. Atorvastatin modulates inflammatory process and reduced LDL –c and CRP by reducing the IL1 and TNFα [39]. A clinical Miracl study which illustrated that Statin reduced 83% CRP from baseline.

DLQI at baseline were 19.6 ± 1.98. The greater health problems occurred in older people where psychological stresses mainly affected younger persons as observed in this study [40]. The mean percentage change of DLQI at the end of six months were 71.05 ± 3.46 in patients. Psoriasis vulgaris exerted negative psychological and social impact on life and health of patients. They have worst effect on their working and limitation in relationship with relatives mainly due to scaling of lesions [41, 42]. The lipid profile including total cholesterol, LDL, HDL and triglyceride were at upper limit. These values showed proatherogenic level of lipid [43]. Therefore psoriasis leads to dyslipidemia which is the most common cause of cardiovascular risk. Various external and internal factors lead to proatherogenic type of lipid profile results. These factors include genetic influence, smoking, sedentary lifestyle, stresses and increase in oxidative injuries which increases morbidity of cardiovascular diseases [44]. The first follow up of laboratory investigations at the third months after the treatment, showed significant difference in lipid profile in patients from the baseline. The mean percentage change of lipid profile showed that Atorvastatin in high doses produced considerable change from baseline, in this study the dose of Atorvastatin is high as 80mg in the first three months followed by 40 mg in the last three months [31, 45].

All safety profile in this study such as LFT, and CPK statically showed non-significant change from baseline to third months and six months. Atorvastatin in low doses and high doses have the same adverse events as in placebo Groups [46, 47]. CURE-ACS trial proved that Atorvastatin 80 mg and 40 mg was safe and well tolerated [48]. The most important function of statin is reduction of T-cell proliferation and MHC-II class expression which is an important mechanism in autoimmune diseases such as psoriasis in relation to cardiovascular events [49].

Conclusion: Atorvastatin can possess a double benefit for patients, firstly it modulates the immune function and inhibits the inflammatory process and secondly protects them against the cardiovascular risk.

Acknowledgement: We have to express our appreciation to the Dr. Moosa Khan, Head of Pharmacology Department of Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan and Dr. Shahnaz Imdad Kehar, Head of Pathology Department of Jinnah Post Graduate Medical Center, Pakistan for sharing their pearls of wisdom with us during the course of this research. We are also immensely grateful to the Pharmacology Department and Pathology Department of Basic Medical Sciences Institute of Jinnah Post Gradua te Medical Center, Karachi, Pakistan for their support and co-operation.

REFERENCES

1. GJArason et al. Primary Immunodeficiency and Autoimmunity: Lessons from Human Diseases. Scandinavian J Immunol 2010; 71(5):317–328
2. Anna Abou-Raya, Suzan Abou-Raya. Inflammation: A pivotal link between autoimmune diseases and atherosclerosis. AUTREV 2006; 00403: 01-07
3. G. Vaudo et al. Precocious intima-media thickening in patients with primary Sjögren'ssyndrome. Arthritis Rheum 2005; 52 (12): 3890–3897.
4. Chung CP et al. Increased coronary–artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005; 52(10):3045–53.
5. M. McMahon, BH Hahn, "Atherosclerosis and systemic lupus erythromatosus—mechanistic basis of the association". Current Opinion in Immunology 2007; 19(6): 633–639.
6. Michelle A et al. Pathogenesis and therapy of psoriasis. NATURE 2007; 445:866-873
7. Gelfand JM et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol 2012; 148(4):487-494.
8. Katzung BG, Masters SB and Trevor AJ. Drugs used in disorders of coagulation In: Basic and clinical Pharmacology, 13th ed, McGraw Hill Education, 2016; 625-627.
9. Octavia Y et al. Doxorubicin-induced cardiomyopathy: From molecular mechanisms to therapeutic strategies. J Molecular and cellular cardiol 2012; 52:1213–1225.
10. Bien S et al. The endothelin receptor blocker bosentan inhibits doxorubicin-induced cardiomyopathy. Cancer Res 2007; 67:10428–35.
11. Riad A et al. Pretreatment with statin attenuates the cardiotoxicity of Doxorubicin in mice. Cancer Res 2009; 69(2):695-9.
12. Shirinsky IV et al. Efficacy and safety of simvastatin for psoriasis vulgaris – a historical control study. VestnikDermatologii I Venerologii 2009; 5: 88-92.
13. Abbas A et al. Rosuvastatin and Atorvastatin: Comparative effects on glucose metabolism in non-diabetic patients with dyslipidaemia. Clin Med Insight Endocrinol Diab 2012; 5:13-30.
14. Pella D et al. Pleiotropic effects of statins. Acta Cardiol Sin 2005; 21:190-198.
15. Rao SK et al. An overview of statins as hypolipidemic drugs. Intern J Pharma Sci Drug Res 2011; 3(3):178-183.
16. Berry G et al. The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's carcinoma patients treated with pegylated liposomal doxorubicin. Ann Oncol 1998; 9:711-716.
17. Karen D et al. Comparative study of methotrexate and cyclosporine in the treatment of psoriasis. NJDVL 2010; 9(1):15-21.
18. Kato AM et al. Serum level of prolactin in psoriatic patients. Egyptian Dermatol Online J 2012; 8(2):1-4.
19. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque – type psoriasis. Dermatol 2005; 210(3):194-199.
20. Rodgers M et al. Etanercept, infliximab and Adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess 2011; 15(10): 1-329.
21. Feldman S, Krueger G. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005; 64(2): 65–68.
22. Jellinger PS et al. AACE Task Force for the Management of Dyslipidemia and Prevention of Atherosclerosis Writing Committee. Endocr Pract 2012; 18(1):1-78.
23. Jain IVK, Lal H. C-reactive protein and uric acid levels in patients with psoriasis. Ind J Clin Biochem 2011; 26(3):309-311.
24. Vadakayil AR et al. Role of C-reactive protein as a marker of disease severity and cardiovascular risk in patients with psoriasis. Indian Dermatol Online J 2015; 6(5):322-325.
25. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19:210-6.
26. Ma C et al. The association between psoriasis and dyslipidaemia: a systematic review. Br J Dermatol 2013; 168(3):486-495.
27. Gowda S et al. A review on laboratory liver function tests. Pan African Med J 2009; 3:1-17.
28. Sathasivam S, Lecky B. Statin induced myopathy. Br Med J 2008; 337:1159-1162.
29. El-Mehy AE et al. Histological and immunohistochemical study on the effect of doxorubicin on the heart of adult albino rat and the possible protective role of an antioxidant. Menoufiya Med J 2008; 21(1):91-108.
30. Gomez-Garre D et al. Resuvastatin added to standard heart failure therapy improves cardiac remodelling in heart failure rats with preserved ejection fraction. Eur J heart Fail 2010; 12:903-912.

31. Ghazizadeh R et al. Clinical improvement in psoriasis with treatment of associated hyperlipidemia. Am J Med Sci 2011; 341(5):394-398.
32. Aurangabadkar SJ. Comorbidities in psoriasis. Indian J Dermatol Venereol Leprol 2013; 79(1):10-17.
33. Bennink RJ et al. Annexin V imaging of acute doxorubicin cardiotoxicity (Apoptosis) in rats. J Nucl Med 2004; 45(5):842848
34. Koti BC et al. Cardioprotective effect of lipistat against doxorubicin induced myocardial toxicity in albino rats. Indian J Exp Biol 2009; 47:41-46.
35. Reich A et al. Apprehension of the disease by patients suffering from psoriasis. Postepy Dermatol Alergol 2014; 31(5):289-293.
36. Dilnawaz M et al. Clinical audit: baseline psoriasis area and severity index (PASI) and dermatology life quality index (DLQI) assessment of psoriasis patients. J Pak Assoc Dermatologists 2013; 23(4):407-411.
37. Faghihi T et al. Atorvastatin for the treatment of plaque-type psoriasis. Pharmacotherapy 2011; 31(11):1045-1050.
38. Ansar A et al. CRP serum level in patients with psoriasis before and after treatment with narrow-band ultraviolete B. J Dermatol Cosmet 2012; 3(1):33-39.
39. Schwartz GG et al. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001; 285(13):1711-1718.
40. Lin T et al. Quality of life in patients with psoriasis in Northern Taiwan. Chang Gung Med J 2011; 34:186-196.
41. Vasiuk IuA et al. Possibilities of Atorvastatin in complex management of extensive psoriasis in patients with arterial hypertension. Kardiologiia 2010; 50(3):37-46.
42. Mattei PL et al. Psoriasis area severity index (PASI) and the dermatology life quality index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol 2014; 28(3):333-7.
43. Dsouza PH, Kuruville M. Dyslipidemia in psoriasis: as a risk for cardiovascular disease. Intern J Res Med Sci 2013; 1(2):53-57.
44. Nakhwa YC et al. Dyslipidemia in psoriasis: A case controlled study. Intern Schol Res Notice 2014; 2014:1-5.
45. Bonnet J et al. Comparative effects of 10-mg versus 80-mg atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study. Clin Ther 2008; 30(12):2298-2313.
46. Newman C et al. Comparative safety of Atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. Ann J Cardiol 2006 ;97(1):61-7
47. Clearfield MB et al. Comparison of the efficacy and safety of Rosuvastatin 10 mg and Atorvastatin 20 mg in high-risk patients with hypercholesterolemia-Prospective study to evaluate the use of low doses of the statins Atorvastatin and Rosuvastatin (PULSAR). Trials 2006; 7:1-11
48. Kaul U et al. Post-marketing study of clinical experience of Atorvastatin 80 mg vs 40 mg in Indian patients with acute coronary syndrome-a randomized, multi-Centre study (CURE-ACS). J Assoc Physicians India 2013; 61(2):97-101.
49. Cristina Ulivieri et al. Simvastatin impairs humoral and cell-mediated immunity in mice by inhibiting lymphocyte homing, T-cell activation and antigen cross-presentation. Eur J Immunol 2008; 38:2832–2844.