**ORIGINAL ARTICLE**

# Role of Ursodeoxycholic Acid in Improving Cholestasis in Patients with Chronic Hepatitis C

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## ABSTRACT

**Aim:** To determine the change in serum liver markers following 600mg daily dose of ursodeoxycholic acid in patients with chronic hepatitis C.
**Design:** The present study was a quasi-experimental study.
**Study settings:** Department of Gastroenterology, Mayo Hospital Lahore from March 2019 to February 2020.
**Methods:** 60 consecutive patients of both genders aged between 20-60 years presenting with chronic hepatitis C were included after written informed consent. Serum levels of ALT, AST and GGT were recorded before starting 600mg of ursodeoxycholic acid daily for 6 months when serum levels of these parameters were assessed again and percent reduction was calculated. An informed written consent was acquired from all the patients.
**Results:** In the present study, the mean age of the study participants was 39.4±9.7 years. There were 42(70%) male and 18(30%) female patients with a male to female ratio of 2.3:1. Ursodeoxycholic acid treatment was found to improve cholestasis with significant decline in serum ALT (119.22±24.28 to 71.50±13.28 IU/L; p-value<0.001), AST (84.78±14.31 to 63.93±14.42 IU/L; p-value<0.001) and GGT (89.10±14.64 to 51.87±14.98 IU/L; p-value<0.001) after 6 months of treatment.
**Conclusion:** A 600mg daily dose of ursodeoxycholic acid was found to improve the cholestasis in patients with chronic hepatitis C which advocates its preferred use in the management of such patients in future medical practice.
**Keywords:** Chronic Hepatitis C, Cholestasis, Ursodeoxycholic Acid

## INTRODUCTION

Viral hepatitis is becoming more and more prevalent and accounts for major share of chronic liver disease along with autoimmune and alcohol induced liver damage[1]. Around 15-20% of cases of acute hepatitis result from viral affection[1,2]. Though majority of the patients recover after acute episode, the proportion of patients who develop chronic illness after hepatitis C is substantially high where almost 50%-80% of patients develop chronic liver damage unless treated[2]. These patients are at higher risk of decompensated liver disease with its systemic complications, hepatocellular carcinoma and death[1,2]. In developing countries including Pakistan, viral hepatitis is far more common than other non-infectious etiologies due to inappropriate public and social practices. Lack of awareness is a major contributor towards many patients presenting with chronic and advanced disease[3,4]. National survey conducted in 2007 – 2008 reported the prevalence of hepatitis C to be 4.8%[3]. Another local study reported the prevalence of chronic hepatitis C to be 11.6% in general adult population, 10.1% among blood donors, 4.7% among pregnant women, 1.6% among children with highest prevalence among injecting drug users i.e. 51.0%[4]. This high burden of disease, its treatment cost as well as disease complications and cost for their medical treatment together put a huge economical burden over the society[3,4]. Therefore there is need for preventive measures to reduce the burden of disease as well as innovation in treatment options to reduce the morbidity and mortality of patients with hepatitis C.

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid which is non-toxic and is routinely used in the treatment of patients with primary biliary cirrhosis and gall-stones disease[5]. Although there is substantial evidence on its role in the management of cholestasis of pregnancy[5], yet only limited studies have investigated its role in the management of patients with chronic hepatitis C[6-8]. Although these studies claimed beneficial role of UDCA among viral hepatitis C patients, yet the evidence was limited and warranted further studies. The present study was therefore conducted with a hope that if oral UDCA supplementation can improve the liver function in patients with chronic hepatitis C, it will enable better management of such patients in future medical practice.

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## PATIENTS AND METHODS

This was a quasi-experimental study carried out at the Department of Gastroenterology, Mayo Hospital Lahore over 1 year from March 2019 to February 2020. Sample size of 60 cases was calculated with 95% confidence level and 80% power of test while taking expected mean of percent reduction in serum GGT to be 25.2±4.4%[6]. Non-probability, consecutive sampling was done and 60 patients of both genders aged between 20-60 years diagnosed of hepatitis C infection in the past 2 years were included into this study after taking written informed consent. Patients

were considered if they had confirmed hepatitis C infection on PCR (polymerase chain reaction). Those with pregnancy, viral hepatitis other than hepatitis C and alcohol induced or autoimmune hepatitis, already receiving hepatitis C treatment or planned for liver transplant were excluded. We also excluded patients receiving corticosteroids, immunosuppressives, cholestyramine or other drugs that might affect liver function. All patients underwent baseline assessment where serum ALT (alanine aminotransferase), AST (aspartate aminotransferase) and GGT (gamma-glutamyl transferase) levels were acquired and recorded. These patients were then advised to take UDCA 600mg/day orally. At the end of 6 months of treatment, serum levels of ALT, AST and GGT were re-assessed and percent reduction from baseline was calculated. Demographic details of the patient along with baseline and follow-up levels of serum liver markers were recorded in a predesigned proforma. All the patients received UDCA of same brand and all the labs were acquired from a single lab to minimize bias while confounders were controlled by exclusion. The collected data was entered into and analyzed through Statistical Package for the Social Sciences (SPSS) version 17.0. Mean±SD has been calculated for numerical variables like age and baseline and follow-up serum ALT, AST and GGT while frequency and percentage has been calculated for gender. Paired sample t-test has been applied to determine the significance of change in serum ALT, AST and GGT after UDCA treatment.

## RESULTS

The age of the patients ranged from 20 years to 60 years with a mean of 39.4±9.7 years. Majority 28(46.7%) of the patients were aged between 31-40 years as shown in Fig. 1. There were 42(70%) male and 18(30%) female patients with a male to female ratio of 2.3:1 as shown in Fig. 2. At the time of start of study, serum ALT level ranged from 71 IU/L to 153 IU/L with a mean of 119.22±24.28 IU/L while the serum AST level ranged from 60 IU/L to 105 IU/L with a mean of 84.78±14.31 IU/L. Serum GGT level ranged from 65 IU/L to 115 IU/L with a mean of 89.10±14.64 IU/L. After 6 months of treatment, a significant decline was observed in these serum parameters with a mean serum level of ALT as 71.50±13.28 IU/L (36.4±21.8% reduction from baseline), AST as 63.93±14.42 IU/L (21.6±24.9% reduction from baseline) and GGT as 51.87±14.98 IU/L (40.8±18.2% reduction from baseline). The observed difference was statistically significant as shown in Table 1.

Fig. 1: Frequency of various age groups in the study sample

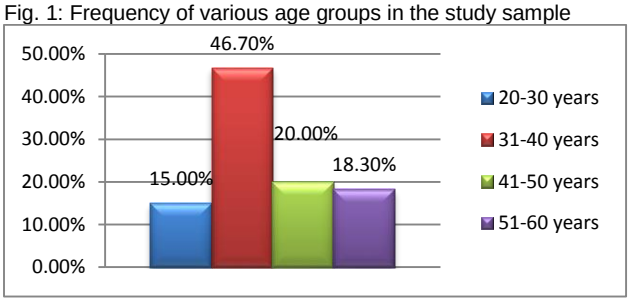


Fig. 2: Gender Distribution of Study Sample

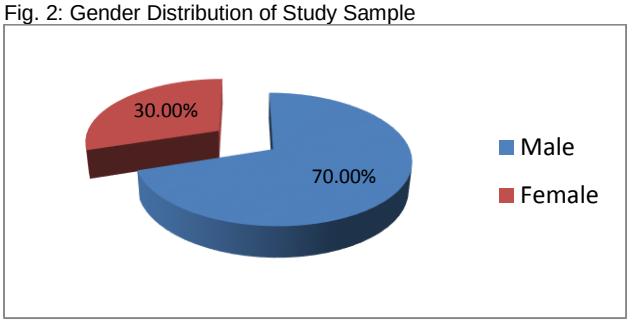


Table 1: Effect of ursodeoxycholic acid treatment on cholestasis

| Serum Parameter | Baseline | Follow-up | P value | Percent Reduction |
|---|---|---|---|---|
| ALT (IU/L) | 119.22±24.28 | 71.50±13.28 | <0.001* | 36.4±21.8 |
| AST (IU/L) | 84.78±14.31 | 63.93±14.42 | <0.001* | 21.6±24.9 |
| GGT (IU/L) | 89.10±14.64 | 51.87±14.98 | <0.001* | 40.8±18.2 |

Paired sample t-test, * observed difference was statistically significant

## DISCUSSION

In patients with intra-hepatic cholestasis, the accumulation of chenodeoxycholic (CDCA) and deoxycholic acids (DCA) is believed to be responsible for progressive liver damage evident from elevation of serum markers like ALT, AST and GGT[5]. Ursodeoxycholic acid has been shown to reduce this liver damage by increasing the hydrophilic fraction along with stabilization of the cell membrane[5,7]. Although, there is a growing trend towards the use of UDCA in the management of patients with chronic liver disease resulting from viral hepatitis[5-8], the existing research evidence to support this practice was limited which necessitated the present study.

In the present study, we observed that the mean age of the patients with hepatitis C infection was 39.4±9.7 years. Iqbal et al.[9] (2013) reported similar mean age of 39.5±8.2 years among patients presenting with hepatitis C disease at DHQ Hospital Dir KPK while Mahmood et al.[10] (2007) reported it to be 39.5±10 year at Lady Reading Hospital Peshawar. A similar mean age of 39.6±9.2 years has been reported among such patients at Ziauddin University Hospital, Karachi by Owais et al.[11] (2015). Jadoon et al.[12] (2014) reported it to be 40.3±10.93 years at Ayyub Teaching Hospital Abbottabad. A similar mean age of 42.32 ±8.5 years was reported by Abbas et al.[13] (2012) among patients undergoing treatment for hepatitis C at Aga Khan University Hospital, Karachi. Sarwar et al.[14] (2017) reported much higher mean age of 49.4±12.1 years among such patients presenting at Doctors Hospital and Medical Center, Lahore.

This observed mean age is much lower than the one reported in literature from other countries. Kowdley et al.[15] (2013), Lawitz et al.[16] (2013) and Pearlman et al.[17] (2015)

reported mean age of 51±9.8 years, 51.4±9.4 years and 55 years respectively in USA while Foster et al.[18] (2015) reported it to be 51±9.7 years in UK. Steinebrunner et al.[19] (2015) reported mean age of 54.8±7.9 years in Germany while Kanda et al.[20] (2017) reported much higher mean age of 62.0±12.5 years in Japanese such patients.

In the present study, we observed that majority (46.7%) of the patients were aged between 31-40 years. Similar higher proportion of this age group has also been observed by another local study where Mahmood et al.[10] reported that 42.5% of such patients at Lady Reading Hospital Peshawar were aged between 31-40 years. Jadoon et al.[12] also reported that 31-40 years age group contributed majority (35.9%) of the patients in their series.

We observed a male predominance among patients with hepatitis C infection with male to female ratio of 2.3:1. A similar male predominance with a male to female ratio of 2.2:1 has been reported by Owais et al.[11] at Ziauddin University Hospital, Karachi while a male to female ratio of 2.5:1 has also been reported by Iqbal et al.[9] at DHQ Hospital Dir KPK. Abbas et al.[13] reported a male to female ratio of 3.3:1 among such patients at Aga Khan University Hospital, Karachi. However, Sarwar et al.[14] (2017) and Akram et al.[21] (2011) reported an equal gender distribution (m:f, 1:1) among such patients at Doctors Hospital and Medical Center, Lahore and Ghurki Trust Teaching Hospital, Lahore respectively. Kowdley et al.[15] reported similar male predominance in USA with male to female ratio of 2:1. Lai et al.[22] (2016) reported much higher male to female ratio of 4.6:1 in Chinese patients with hepatitis C infection while Kanda et al[20] reported it to be 1:1 in Japan.

In the present study, we observed that ursodeoxycholic acid treatment in hepatitis C patients significantly improved the cholestasis evident from significant reduction in serum ALT, AST and GGT levels after 6 months of treatment. Our observation is in line with a similar previous study where Omata et al. (2007) treated 200 Japanese hepatitis C patients with 600 mg ursodeoxycholic acid daily. They too reported similar significant improvement in serum ALT (106.3±59.4 to 75.7±41.9 IU/L; p-value=<0.001; percent reduction=29.2%), AST (82.4±41.8 to 63.1±32.9 IU/L; p-value<0.001; percent reduction=25%) and GGT (82.4±62.2 to 49.7±43.0 IU/L; p-value<0.001; percent reduction=41%) after 6 months of treatment. Similar beneficial effects of ursodeoxycholic acid treatment among hepatitis C patients has been confirmed in another Japanese study where Sato et al (2009) observed 22.1% reduction in ALT and GGT and 19.1% reduction in AST.

The present study is first of its kind in local population and adds to the limited already published research evidence on the topic. The strengths of the present study were its large sample size of 60 cases and strict exclusion criteria. We observed relatively younger mean age among such patients in local population as compared to developed countries which raises serious concern on public health awareness, practice and policies. It also warrants public health measures to counteract this alarming situation. Also, in the present study, this novel treatment with 600mg of ursodeoxycholic acid was found to improve the cholestasis in chronic hepatitis C patients and may thus improve the outcome of treatment among such patients. Though these results favor the use of this novel therapy in future practice, there is need for future studies comparing combined effect of ursodeoxycholic acid along with interferon. This information would further help in the selection of more appropriate treatment plan in patients with chronic hepatitis C. Such a study is highly recommended in future clinical research.

## CONCLUSION

A 600mg daily dose of ursodeoxycholic acid was found to improve the cholestasis in patients with chronic hepatitis C which advocates its preferred use in the management of such patients in future medical practice.

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