Medicine Science 2016;5(1):209-21 Danazol and Thrombocytopenia in ChronicHepatitis C

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Danazol one Month Treatment of Thrombocytopenia in Chronic Hepatitis C

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Abstract

Thrombocytopenia is frequently observed in patients with chronic hepatitis C virus. Moderate and severe thrombocytopenia (<75,000/mm³) may interfere with diagnostic or therapeutic elective procedures and can be a limiting factor when considering these interventions. The aim of this study was to evaluate the efficacy of one month Danazol treatment for increasing and maintaining platelet levels in chronic hepatitis C virus patients associated with thrombocytopenia. 48 patients with chronic hepatitis C virus and platelet levels less than 75000/mm³ were included. Danazol was given in conventional dose 400 mg (200 mg bid) per oral after meal for one month, the monitoring of platelet levels was performed during treatment, at the end of treatment and at three months after the end of treatment. After one month with Danazol treatment the mean platelet levels increased significantly from 60400 + 11100/mm³ to a level of 90700 + 31400/mm³. Danazol increased the platelet levels of 33 (68.8%) patients more than 75000/mm³ and 5 (10.4%) patients had an increase in platelet levels but did not exceed 75,000/mm³, while in 10 (20.8%) patients platelet levels declined and considered unresponsive to Danazol. The percentage of patients with moderate thrombocytopenia (50000 to 75000/mm³) decreased significantly from 83.3% to 20.8% after Danazol treatment. Danazol one month treatment is effective for increasing and maintaining platelet levels and can be considered a treatment option for thrombocytopenia in chronic hepatitis C virus.

Keywords: Danazol, chronic hepatitis C virus, thrombocytopenia

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Introduction

Thrombocytopenia (platelet level less than 150000/mm3) is frequently observed in patients with chronic HCV (0.16% to 45%) [1], often believed to be due to hypersplenism or splenic platelet sequestration however, thrombocytopenia has been observed in HCV without evidence of cirrhosis or splenomegaly. Patients with HCV seem to develop lower platelet levels than patients with other causes of cirrhosis due to bone marrow suppression either by HCV directly, or immune-mediated platelet destruction involving anti-platelet antibodies and/or immune complex associated platelet clearance [2,3] and impaired thrombopoietin production or activity resulting from hepatocellular damage [4,5].

The clinical significance of mild thrombocytopenia (75000–150000/ mm3) is minimal and usually does not interfere with the management and treatment decisions in patients with chronic liver diseases, while moderate and severe thrombocytopenian (<75,000/mm3) could be a limiting factor when considering diagnostic or therapeutic elective procedures in patients with chronic HCV such as liver biopsy, band ligation or surgery due to the increase risk of bleeding. The ability to increase platelet counts could also significantly reduce the need for platelet transfusion [2,3].

Danazol is derivative of synthetic steroid ethisterone [6]. It's well tolerated treatment of refractory autoimmune thrombocytopenia associated with many autoimmune diseases [7]. It has been shown that Danazol may modulate expression of Fc-γ receptors on mononuclear phago-cytes, thereby impending opsonization and destruction of platelets and reduces GP II b - III a complex in patients with autoimmune thrombocytopenia [8,9]. It may also have an immunomodulatory function which can affect anti-platelet antibody production [10].

There are some reports regarding hepatotoxic effects of Danazol after more than 2 years of use, but no reports of adverse effects during short time periods [11,12].

The aim of this study was to evaluate the efficacy of one month Danazol for increasing and maintaining platelet levels in chronic HCV patients with thrombocytopenia.

Materials and Methods

This study was conducted in Out-patient Clinics of Tropical Medicine Department, Faculty of Medicine, Zagazig University Hospitals, between April 2014 and July 2015, 48 patients with chronic HCV and thrombocytopenia less than 75000/mm^3 were selected, as below this level thrombocytopenia may interfere with diagnostic or therapeutic elective procedures.

Exclusion criteria were as follows: concomitant hepatitis B virus infection, renal improvement, pregnancy, breast feeding, autoimmune disease, decompensated cirrhosis, Danazol hypersensitivity, autoimmune thrombocytopenia, autoimmune thrombocytopenia or thromboembolic history. Cirrhosis (compensated in Child-Pugh A or B) was diagnosed in correlation with clinical and ultrasound studies. This study was carried out in accordance with the World Medical Association code of ethics (Declaration of Helsinki), and a written informed consent was obtained from all patients. The protocol was approved by a review board of Tropical Medicine Department of Zagazig University.

A prospective clinical study was conducted on 48 patients with chronic HCV not under any specific antiviral treatment with platelet levels <75000/mm3, Danazol was given in doses of 400 mg (200 mg bid oral) after meal for one month. The response (increase of basal platelet levels) was assessed at 2 weeks, at the end of treatment and at 3 months after the end of treatment.

Danazol treatment was stopped if serious adverse effects occurred, e.g. jaundice or hypersensitivity reaction. All patients underwent the following at the start of treatment: history taking, clinical status assessment, complete blood picture (CBC), liver function tests and kidney function tests. At 2 weeks, at 1 month and at 3 months after the end of treatment, the previous investigation was repeated. Adherence to treatment was monitored through interviews with patients weekly.

The collected data were coded and analyzed using SPSS version 16.0. For quantitative data mean, median, slandered deviation and range were used for summarization, while ANOVA (analysis of variance), repeated t test and post hoc test were used for analysis .For

qualitative data; number of observation and percentage of each category were used for summarization while Chi-square test and Macnemar test were used for analysis. The sample size was calculated using Epi-Info version 6 at power of study, 80% and 95% confidence interval and the level of significance <0.05 as 48 patients who fulfill the inclusion criteria. A P-value less than 0.05 were considered statistically significant.

Results

The A total of 48patients (28 males and 20 females) with chronic HCV and thrombocytopenia <75000/mm3 were included and were given 400 mg Danazol for 1 month. The mean age was 39.30 + 8.7(range 28-60 years) 28 male and 20 female (Table 1). One patient developed mild cholestasis after 2 weeks, Danazol was stopped and the patient received ursodeoxycholic acid 15 mg/kg per oral and improved.

From table 2, 38 patients (79.2%) responded to Danazol and their basal platelet levels increased, 33 patients (68.8%) from them got levels more than 75000/mm3 and 10 (20.8%) patients did not show any increase in their platelet levels over one month treatment and were considered to be non responders. The mean of platelet levels of all patients had increased significantly from the base time level of 60400 + 13000/mm3 (40000-74000) to a level of 90700 + 14000 /mm3 (65000-14000) at the end of treatment and had decreased to 82400 + 11000 /mm3 (49000-12000) at 3 months after the end of treatment but not statistically significant as shown in table 4 and figure 1.

Table 3 shows that the percentage of patients with moderate thrombocytopenia had decreased significantly after Danazol treatment from 83.3% to 20.8%.

Table 4 shows also that no statistically significant changes or differences in biochemical parameters after Danazol treatment and after 3 months follow up except significant decrease of serum albumin only after treatment. Table (5) shows that the patients younger than 50 years and females had a significantly higher probability of achieving response to Danazol than older patients and males with odds ratio 19.6 and 1.2 respectively.

All the patients tolerated Danazol treatment, the most common side effects were nausea 3(6.25%), vomiting 2 (4.2%) and abdominal pain 2 (4.2%) as shown in table 6 and most of them were mild. The patients with cirrhosis did not show any manifestations of decompensation during treatment or the follow up period.

Table 1. Demographic characteristics of the patients

Data	N= 48 Patients
Age (years)	
Mean ± SD	39.30 ± 8.7
Range	28 – 60
Gender (%)	
Male	28 (58.3%)
Female	20 (41.7%)
Body mass index (BMI)	
Mean ± SD	25 ± 3
Range	23 – 32
Diagnosis	
Chronic HCV	35 (72.9%)
Cirrhosis due to HCV	13 (27.1%)

Table 2. The mean platelet levels at the base time, at the end of treatment and after 3 month from the nd of treatment**.**

Response to Danazol	End of treatment [N (%)]	After 3 months [N (%)]	**P**
-Responder (increase platelet level)	38 (79.2%)	35 (72.9%)	0.05*
Responder to level >75x10^3/mm^3	33 (68.8%)	28 (56.5%)	
Responder to level <75x10^3/mm^3	5 (10.4%)	7 (14.6%)	
-Non responder (decline platelet level)	10 (20.8%)	13 (27.1)	

*P<0.05: Significant.

Table (3): Number of patients in relation to severity of thrombocytopenia before and after treatment

	Before Danazol		**After Danazole**		
	No	**%**	**No**	**%**	**P**
Less 50000/mm^3	8	16.7	5	10.4	0.25
From 50000/mm^3 to 75000/mm^3	40	83.3	10	20.8	0.00*
More than 75000/mm^3	-	-	33	68.7	0.00*

*P<0.05: Significant.

Table 4. Comparison between biochemical parameters of patients at base time, at end of treatment and at 3 months after end of treatment

	Base time Mean ± SD	End of treatment Mean ± SD	After 3 months Mean ± SD	P
Platelet level(/mm$^{3)}$	60400 ±13000 [a] (40000-74000)	90700 ± 14000[b] (65000-14000)	82400 ± 11000 [b] (49000-12000)	0.00*
Hemoglobin (gm./dl)	12.7 ± 0.7	12.1 ± 0.75	11.8 ± 0.9	0.53
WBCs (× 10²)	6.7 ± 1.7	7.6 ± 1.5	7.1± 1.3	0.47
ALT (UI/L)	68.3 ± 11.8	70.3 ± 10.7	67.9 ± 10.8	0.54
AST (UI/L)	60.0 ± 11.7	60.4 ± 8.9	65.5± 5.8	0.47
Alkaline phosphatase (UI/L)	105.3 ± 22.6	106.7 ± 20.4	106.1±19.7	0.39
Totalbilirubin(mg/dl)	0.79 ± 0.2	1.0 ± 0.1	1.1± 0.09	0.57
Albumin (gm./dl)	4.0 ± 0.1[a]	3.7 ± 0.01[b]	3.9 ± 0.2 [b]	0.02*
INR	1.2 ± 1.2	1.3 ± .02	1.1± 0.3	0.74
Creatinine (mg/dl)	0.9 ± 0.12	0.9 ± 0.1	0.9 ± 0.2	0.87
Cholesterol (mg/dl)	171.6 ± 16.0	181.5 ± 18.7	157.2 ±16.7	0.25
Triglycerides (mg/dl)	95.6 ± 30	97.4 ± 12.2	97.4 ± 10.5	0.75
Body mass index	26.9± 2.8	27.3± 2.4	26.9 ± 2.8	0.37
CTP score	5.6 ± 1.2	5.6 ± 0.8	5.5 ± 0.7	0.87

† Means of the same alphabet shows no significant difference e.g. (a-a/b-b) but different subsets (a-b-c) shows significant difference. * P<0.05: Significant. ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, INR: International normalized ratio. CTP: Child Turcotte- Pugh

Table 5. Predictors of Danazol response

Parameters	Total [N (%)]	Response [N (%)]	Odds Ratio	P
Age:				
- **≤50 years**	28 (58.3%)	27 (96.4)	19.6	0.00*
- **>50 years**	20 (21.7%)	11 (55%)		
Gender:				
- **Male**	28 (58.3%)	21 (42.8%)	1.2	0.04*
- **Female**	20 (21.7%)	17 (85%)		
Platelet level:				
- **≤ 50000 / mm³**	8 (16.7%)	5 (62.5%)	0.30	0.14
- **> 50000 / mm³**	40 (83.3%)	33 (84.6%)		
Body mass index (BMI):				
- **18 - 24.9**	9 (18.9%)	5 (55.5%)	1.4	0.23
- **25 - 29.9**	28 (58.3%)	26 (92.8%)	81	
- **>30**	11 (22.9%)	7 (63.6%)	11.3	
Spleen size				
- **≤ 13cm**	17 (35.4%)	16 (94.1%)	6.5	0.13
- **> 13cm**	31 (64.6%)	22 (70.9%)		
Diagnosis:				
- **Cirrhosis**	10 (20.8%)	29 (76.3%)	0.82	
- **Chronic hepatitis C**	38 (79.2%)	9 (90%)		0.57

* P< 0.05: Significant

Table 6. Adverse effects during treatment with Danazol

Side effects	N= 48Patients
Jaundice	2 (4.2%)
Non specific GIT symptoms	
Abdominal pain	2 (4.2%)
Nausea	3 (6.3%)
Vomiting	2 (4.2%)
Hypersensitivity	1 (2.1%)

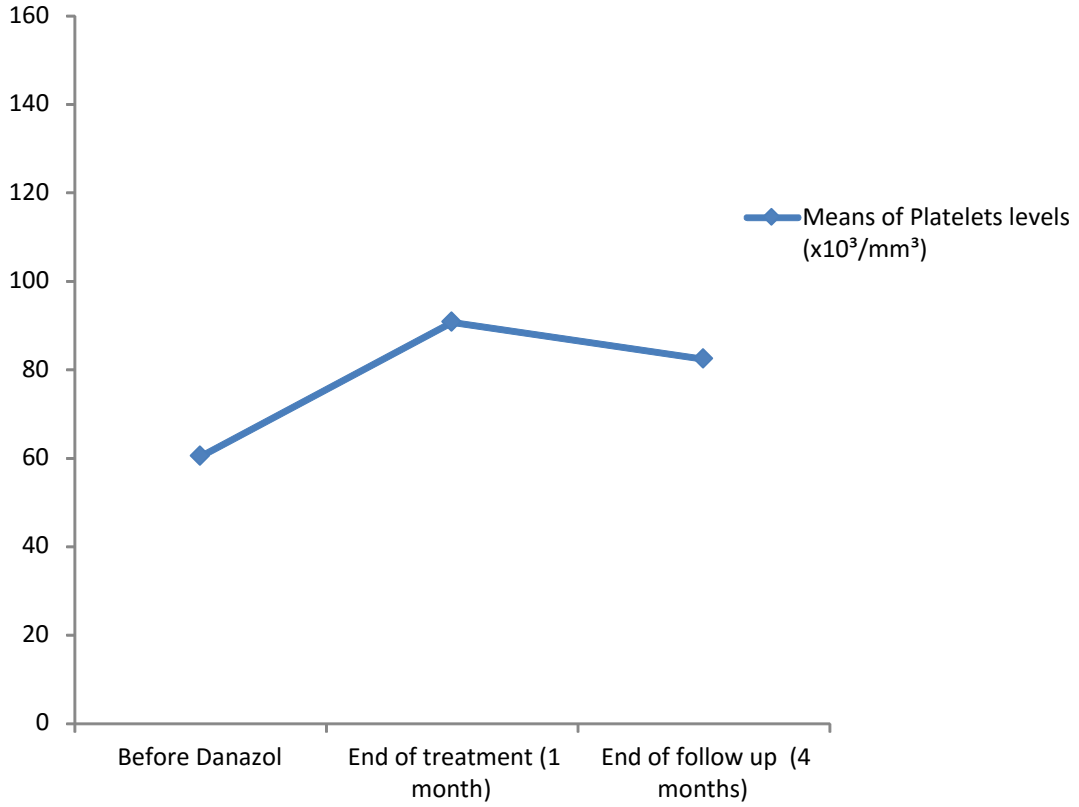

Figure 1. Changes in platelets levels before Danazol treatment, at end of treatment and after 3months follow up. The points represent mean values of patient's platelet levels and the line represent behavior in platelet levels with time .

Discussion

Thrombocytopenia is frequently observed in patients with chronic HCV and can limit many diagnostic and therapeutic procedures with increased risk of bleeding. The aim of this clinical trial was to evaluate the efficacy, tolerability and safety of one month Danazol in increasing and maintaining platelet levels in chronic HCV and compensated cirrhosis due to HCV.

The present study included 48 patients with chronic HCV and thrombocytopenia less than 75000/mm3. We consider this platelet level because below this level many procedures could not be done to chronic HCV patients due to the risk of bleeding, which increases with more decrease in platelet level while mild thrombocytopenia (>75000/ mm3) has a low risk of bleeding.

Alvarez et al. [7] included 49 patients with chronic HCV and thrombocytopenia ≤ 90000/mm3 because patients were included during Pegylated Interferon (Peg IF) treatment and Danazol was given as long as they were still under treatment to prevent stoppage or decrease anti-viral treatment. In the present study, Danazol 400 mg for one month was given on the basis of least effective and safe dose and also for a short time (one month) to minimize risk of severe or undesirable adverse effects and to facilitate any intervention diagnostic or therapeutic procedures by elevation of platelet levels over a short a short time. The ability to increase platelet levels could significantly reduce the need for platelet transfusions and facilitate the use of other medication indicated treatments in patients with liver disease [3].

Danazol increased platelet levels to 90700 + 31400/mm3 from base time level of 60400 + 11100/mm3 with response rate 79.2% (38 patients). In Alvarez et al. study [7] Danazol result in a higher response rates (85%) and higher platelet levels (121081 + 47320/mm3), this could be explained by longer treatment period (2-11 months), higher basal platelet levels as they included levels ≤ 90000/mm3 and also Danazol 600 mg dose with used for patients with platelet level ≤ 60000/mm3 from the start.

The exact mechanism of Danazol on autoimmune thrombocytopenia is still unknown, but the present results suggest that HCV associated thrombocytopenia has, at least in part, an autoimmune mechanism [2,3] and Danazol might prevent platelet destruction. West and Jonson [9] found Danazol treatment is effective in autoimmune thrombocytopenia with

systemic lupus erythrymatosis and thrombocytopenia improved in 6 weeks of Danazol treatment and this was in concordance with one month duration, in this study and clarifies efficacy of short term Danazol treatment of thrombocytopenia.

Thrombopoetin mimics (Romiplostin, Eltrombopag) are TPO -Receptor agonists, which act through increase production of platelets [13]. The use of Eltrombopag in HCV patients with thrombocytopenia is cost-effective [14]. Eltrombopag increased safely platelet levels in dose dependent manner in HCV related compensated liver diseases with thrombocytopenia over 4 weeks of therapy [15,16] but, although this patient must be well monitored to prevent possible thromboembolic or bone marrow complications or liver failure occurrence [17]. In our clinical study, Danazol administration has decreased significantly the percentage of patients with moderate thrombocytopenia over one month with a maintaining effect for 3 months after stoppage of treatment as platelet levels decrease. But, still significantly higher than basal level and accepted for some diagnostic or therapeutic elective surgical procedures. One patient had mild cholestasis and improved after stoppage Danazole otherwise, most of the adverse effects with Danazol treatment in this study were mild and required no treatment. Danazol had no significant affection on liver, kidney functions, serum lipids or body mass index. Patients with compensated cirrhosis did not show any manifestation of decompensation during or after Danazole treatment which emphasis safety at this dose and duration for chronic compensated HCV.

Conclusion

Danazol one month treatment is effective for increasing and maintaining platelet levels in chronic HCV and it can be considered a treatment option for thrombocytopenia in HCV compensated liver diseases.

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