Prolonged use of pentoxifylline increases the life expectancy of patients with compensated cirrhosis: A 20-year retrospective study

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Abstract. Liver cirrhosis is a pathology of varied etiology with a high prevalence and mortality, resulting in >1 million mortalities per year. Patients with liver cirrhosis typically have a survival time of 12 years following diagnosis. The treatment for this disease is directed at the complications of cirrhosis; however, to the best of our knowledge, the long-term management of patients with cirrhosis has been scarcely studied. Pentoxifylline (PTX) is a non-selective phosphodiesterase inhibitor with rheological activity and antioxidant, anti-inflammatory and antifibrotic properties. PTX has been used in the treatment of peripheral arterial disease, inflammatory liver diseases and hepatocellular carcinoma with encouraging results. The aim of the present study was to evaluate the effect of PTX use on the survival of patients with compensated cirrhosis. For this purpose, a cross-sectional study was performed at the Gastroenterology and Hepatitis C Department of Dr. Valentín Gómez Farias Hospital (Institute for Security and Social Services for State Workers, Zapopan, Mexico) from June, 1996 to December, 2019. The follow-up time for these patients was 22.6 years (up to the end of the study period). In the present study, 326 patient files were analyzed and 118 patients with the disease were identified, 81 of whom (68.64%) died within 12 years after diagnosis. Of the included patients, 26 received PTX combined with PEG IFN-α-2a plus ribavirin, and 11 received PTX plus propranolol, with a median treatment duration of 20.6±0.8 years. Furthermore, 16 patients (43%) did not develop co-morbidities within this time, and the transition to decompensated cirrhosis was 16.6 years, with a survival time of 20 years. Therefore, the results of the present study suggest that PTX may improve the long-term survival of patients with compensated cirrhosis, rendering PTX a candidate for repurposing in the treatment of hepatic cirrhosis.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HSC, hepatic stellate cells; LSEC, liver sinusoidal endothelial cells; MMP, matrix metalloproteinases; NF-κB, nuclear factor κB; PTX, Pentoxifylline; Tbili, total Bilirubin; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor-α; TP, total proteins

Key words: hepatic cirrhosis, fibrosis, pentoxifylline, survival

Introduction

Liver cirrhosis is characterized by fibrosis of the liver secondary to chronic injury, which leads to an alteration in the normal lobular organization of the liver. Cirrhosis is a clinically significant affliction that has an impact on the morbidity and mortality of patients (1,2). Cirrhosis is typically classified as compensated or decompensated. In compensated cirrhosis, the liver can maintain its important functions and patients can remain asymptomatic for the first few years, until diagnosis (3). In decompensated cirrhosis, abnormal liver function test results are observed (including elevated serum transaminase) and patients develop notable health problems (including jaundice, bleeding varices in the esophagus, ascites and hepatic encephalopathy) (4). The median survival time of patients with compensated cirrhosis is <12 years. By contrast, in decompensated cirrhosis, the median survival time

is 2-4 years, with a rate of transition of 5-7% each year (5). Liver cirrhosis is a notable health problem and its prevalence is difficult to estimate as patients often present in the advanced stages of disease; thus, the incidence of this disease may be underestimated. The incidence of liver cirrhosis in Europe is estimated to be 26 cases per 100,000 individuals; in Asia, its prevalence is 16-23 cases per 100,000 individuals (6,7). Liver cirrhosis affects both sexes, predominantly between the ages of 40 and 60 years old. The majority of patients die within 12 years (8), on average and, based on the Global Burden of Liver Disease 2023, >2 million individuals die annually from this disease, citing it as the 14th leading cause of death (9-11). In Mexico, liver cirrhosis is the sixth leading cause of mortality, with a case fatality rate of 34.2 per 100,000 individuals and an incidence of 3.7% (12-14).

There are multiple etiological causes of cirrhosis that vary geographically. For instance, in Western countries, alcoholism, metabolic-associated fatty liver disease, alcoholic liver disease and hepatitis C virus (HCV) infection are the most common causes (15). By contrast, chronic hepatitis B virus (HBV) infection is the primary cause of liver cirrhosis in the Asia-Pacific region (16). Other less common causes of liver cirrhosis include hemochromatosis (17), Wilson's disease (18), primary sclerosing cholangitis (19), primary biliary cirrhosis (20) and autoimmune-related cirrhosis (21). However, it is considered that ~60% of liver cirrhosis cases have an alcoholic origin (22,23), and that 24% have non-alcoholic origins (7,24). Chronic liver disease is a progressive deterioration of liver function characterized by inflammation leading to fibrosis, cirrhosis and hepatocarcinoma. Hepatic fibrosis is the formation of a fibrous scar that results from the accelerated production of extracellular matrix components for myofibroblasts and hepatic stellate cells (HSCs) (25,26). Furthermore, liver fibrosis results from chronic liver injuries such as hepatotoxic injury caused by chronic HBV and/or HCV infections and immoderate alcohol consumption or metabolic syndromes that induce non-alcoholic fatty liver disease (NAFLD), characterized by liver steatosis exceeding 5% that can progress to non-alcoholic steatohepatitis (NASH) which is characterized by liver injury caused by excessive liver fat, inflammation and faster fibrosis progression, which can lead to cirrhosis and liver cancer (27).

Managing liver cirrhosis depends on the cause and extent of liver damage (28). The goal of treatment is to delay the progression of disease in the damaged liver by treating the etiological factors that contribute to the chronic injury and to decrease the production of proinflammatory or profibrogenic cytokines. The latter is the most direct and perhaps the most effective method of treating liver fibrosis (4). The treatment options include inhibition of HSC activation, HCV- and HBV-specific treatments, weight loss, maintaining healthy levels of blood sugar and lipids, no alcohol intake and anti-inflammatory and immunosuppressive therapies (29). In addition, a number of studies have been conducted using antifibrotic drugs such as silymarin (30), vitamin E (31) and obeticholic acid (32). Combination therapy may be convenient in terms of treating the etiologic, metabolic, anti-inflammatory and antifibrotic aspects of the disease (33).

Pentoxifylline (PTX) is a methylxanthine derivative and a non-specific phosphodiesterase inhibitor. PTX was approved by the U.S. Federal Drug Administration in 1984 for treating leg pain due to claudication (34). Several preclinical and clinical studies have provided evidence that PTX has potent anti-inflammatory and antifibrotic properties (35,36). PTX inhibits the NF-κB transcription factor, decreasing the proinflammatory cytokine levels in the liver (37). PTX can decrease pulmonary fibrosis in patients who are administered chemotherapy and radiotherapy (38), and is potentially effective in treating NAFLD (39,40). Additionally, PTX exhibits an anti-tumor effect in hepatocellular carcinoma (41). The present study aimed to evaluate the improvement in the survival of patients with compensated cirrhosis administered long-term PTX.

Patients and methods

Patient selection. The present study was approved by the Biomedical Research Ethic Committee of Dr. Valentín Gómez Farías General Hospital (Institute for Security and Social Services for State Workers, Zapopan, Mexico; approval no. ISSSTE/CEI/019/08). Due the retrospective nature of the study, the patient consent exemption was approved. In the present study, the clinical data of patients diagnosed with compensated liver cirrhosis between April 1, 1995, and May 31, 1996 and treated from June, 1996 to December, 2019 at the Gastroenterology and Hepatitis C Department of Dr. Valentín Gómez Farias Hospital were retrospectively reviewed. The inclusion criteria were as follows: i) Patients diagnosed with compensated liver cirrhosis, according to Child-Pugh class A (42) (no evidence of ascites and encephalopathy), regardless of age and sex; ii) complete medical record information available with liver disease categorization and histological and serological results; and iii) patients treated with PTX alone or in combination with any other drug. The exclusion criteria were as follows: i) Patients with decompensated cirrhosis (Child-Pugh class B or C); ii) patients with other active malignancies; and iii) incomplete medical record information. Patients were followed up until death or at the end of the study period (December 2019).

Data collection. The demographical (including age and sex), clinical and laboratory data were collected from the medical records. The etiological characteristics, including HCV, HBV and Human Immunodeficiency Virus infection, autoimmunity and alcohol consumption, were also obtained from the medical history of the patient. The laboratory analyses data included platelet count and liver enzyme tests for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), total bilirubin (TBili) and albumin. In total, authors AEJP, ABH and JAGO conducted the data extraction: One author extracted the information and compiled the items of interest, the second author then reviewed and double-checked the information for each of the extracted items and a third author verified the accuracy. Following this, authors MAJL and ABC analyzed the files and data.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation. In certain cases, Δ% was determined, which represents the percentage increase or decrease relative to the value obtained at baseline determination. Group differences were determined by the Mann-Whitney U test.

P<0.05 was considered to indicate a statistically significant difference. Data were analyzed using the SPSS statistical software program (version 25.0; IBM Corp.).

Results

Description of the baseline demographic and clinical data. The medical records provided information from 1996 to 2019. A total of 326 medical records of patients diagnosed with cirrhosis were reviewed in the present study. Of these, 208 were excluded due to decompensated cirrhosis or active malignancies and incomplete medical records, leaving 118 patients included in the analysis. Basic characteristics include liver cirrhosis class A without ascites and encephalopathy, and their age, sex, medical record information and serological results were obtained. The patients were treated with PTX two months after their first diagnosis. During the study period, 81 patients (68.6%) died within 12 years following diagnosis. The diseases of the patients varied, including complications such as decompensation, sepsis, bleeding, lack of treatment adherence and death from accident or cardiovascular diseases. Finally, the data of 37 patients with Child-Pugh Class A cirrhosis who were treated with PTX in combination with other drugs were analyzed. The median treatment time of 20.6±0.8 years. The median age of the patients was 60.5 years. The majority of patients were female (70%; n=26), and the remaining 11 (29.7%) were male. The follow-up time for these patients was 22.6 years (up to the end of the study). The baseline characteristics of the study group are shown in Table I. The etiologies of liver cirrhosis in the included patients were HCV in 26 (70%) patients, alcohol in 6 (16%) patients, NASH in 3 (8%) patients, autoimmune hepatitis in 1 (3%) patient and HBV in 1 (3%) patient. During the follow-up period, the patients attended scheduled appointments every 3 months for laboratory PCR evaluation (HCV load). In addition, echo-sonograms were conducted every 6 months, and baseline endoscopic studies were scheduled every year for patients with a history of bleeding.

Clinical treatments. In total, 26 (70.2%) patients were treated with PTX + PEG IFN-α-2a + ribavirin (400 mg/12 h orally + 180 μg/week subcutaneously + 800-1,200 mg/day orally with varying doses, respectively), while the remaining 11 (29.7%) patients were treated with PTX + propranolol (400 mg/12 h orally and 80 mg/day) (Table I). Of the HCV-infected patients treated with PTX, 57.6% did not respond to treatment compared with 42.3% who did respond. Adherence to therapy was 100%, and only 3% (n=8) of patients who received PTX + propranolol experienced nausea and vomiting as a side effect of treatment; nonetheless, these patients did not interrupt their treatment. It was found that nearly 56.7% of patients developed at least one additional comorbidity 20 years following cirrhosis diagnosis. The most prevalent conditions were diabetes mellitus in 6 (16.2%) patients, hypothyroidism in 5 (13.5%) patients and hepatocarcinoma in 5 (13.5%) patients. Furthermore, 16 (43%) patients did not develop co-morbidities within 20 years (Table II).

Liver enzyme levels. Table III shows the liver function test data. In the 37 included patients, elevated AST and TP levels (Δ%=141 and 11, respectively) were found. These levels differed significantly from that of the baseline (P<0.01). An increase in TBili levels (Δ%=31; P<0.01) was also observed, while the ALT, platelets and albumin levels showed no significant changes.

Influence of PTX after 20 years. The clinical evolution of patients with compensated liver cirrhosis is depicted in Table IV. At the data cut-off (December, 2019), 10.8% of patients did not progress and continued in Child-Pugh class A, 24.3% had class B and 64.8% of patients progressed to class C. The decompensation events in the patients included ascites in 29 patients and hepatic encephalopathy in 24 patients. The median time between the diagnosis of compensated and decompensated cirrhosis was 16.6 years. These data demonstrated that the disease progressed slowly in ~64% of patients. The median survival time was 19.7 years (lowest limit for both sexes) to 21.6 years (upper limit) for men and 20.3 years (upper limit)

Table I. Baseline clinical characteristics of patients with cirrhosis.

Etiology	No. of cases (n=37)	%
HCV	26	70
Alcohol	6	16
Non-alcoholic steatohepatitis	3	8
Autoimmune hepatitis	1	3
HBV	1	3
States of cirrhosis		
Compensated	37	
Child Plug A	37	
Ascites	0	
Encephalopathy	0	
Treatments		
PTX + PEG IFN-α-2a + ribavirin	26	70.2
PTX plus propranolol	11	29.7

HCV, hepatitis C virus infection, HBV, hepatitis B virus infection. PTX, pentoxifylline, PEG IFN-α-2a, peginterferon α-2a.

Table II. Comorbidities development in patients with cirrhosis.

Types of comorbidities	No. of cases (n=37)	%
Diabetes mellitus	6	16.2
Hypothyroidism	5	13.5
Hepatocarcinoma	5	13.5
Cerebrovascular event	2	5.4
Sjögren syndrome	2	5.4
Alcoholism	1	2.7
Total	21	56.7
Non-comorbidities	16	43.2

Table III. Laboratory characteristics of 37 patients with non-decompensated cirrhosis treated with pentoxifylline.

Variable	Baseline	End of study	Δ%	P-value
ALT, IU/dl	76.1±45.3	66.7±38.7	-12	NS
AST, IU/dl	20.7±1.7	49.9±24.3	141	0.01
Platelets, $10^3/\mu$l	117.9±30.2	122.7±60.7	4	NS
TP	7.0±0.2	7.8±0.5	11	0.01
Albumin	3.2±0.5	3.3±0.5	3	NS
TBili, mg/dl	1.6±0.3	2.1±0.7	31	0.01

Δ%, percentage increase or decrease in terms of baseline; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total proteins; TBili, total bilirubin; NS, not significant; IU, international units.

Table IV. Clinical evolution and survival of patients with liver cirrhosis treated during 20 years with PTX.

States of cirrhosis	No. of cases (n=37)	%	Survival lower limits/upper limits (years)	Historical survival background[a] (mean ± SD)	End of the study for both sexes (mean ± SD)	Δ%	P-value
Compensated	4	10.8					
Decompensated	33	89.2					
Ascites	33	89.2					
Encephalopathy	33	89.2					
Child-Pugh class[b]							
Class A	4	10.8					
Class B	9	24.3					
Class C	24	64.8					
Males			19.7/21.6	11.3±0.3	20.3±0.8	80	0.0001
Females			19.7/20.3				

To begin the study, the 37 patients had classification A state of Child Pug classification. [a]mean ± SD. [b]All patients beginning the study as class A in the Child-Pugh classification;. SD, standard deviation; Δ%, percentage of increase or decrease in terms of the historical background (historical survival trends of patients with compensated cirrhosis).

for women; these results were statistically significant when compared with the historical survival trends of patients with compensated cirrhosis (historical background) (P<0.0001; Table IV). The number of life-years gained by the patients treated with PTX represented Δ%=80. This result was notable since overall survival comprises the 'gold standard' endpoint of clinical studies. It is important to note that independent studies by D´Amico *et al* (2006) (8), Zipprich *et al* (2012) (43), Asrani *et al* (2013) (1) and Goldberg *et al* (2022) (44) reported 12-year survival rates for patients with compensated cirrhosis. This contrasts with the report of Ginés *et al* (1987) (45), which projected a survival rate of only 8.9 years. In these articles, the authors discussed the natural history of compensated cirrhosis, including predictors and survival rate, and provided a better understanding of disease progression. These papers are some of the most cited in the field.

Discussion

Despite advances in medical care and additional expenditure in the treatment of liver cirrhosis, the mortality rate has increased (46). Patients with liver cirrhosis have a life expectancy of 2-12 years. In the present study, 37 of the 118 patients with compensated liver cirrhosis were treated with PTX. The most notable observation of the present study was the increased life expectancy in patients treated with PTX, which was 20 years; this represented an increase of Δ%=80 in life-years, compared with the overall survival time of the historical background and with those 81 (68.6%) patients who died within the first 12 years following a cirrhosis diagnosis, which was consistent with that previously reported (1,5,43,44).

The comorbidities of patients with cirrhosis include other diseases that are not caused by cirrhosis but comprise risk factors that increase mortality. In this regard, 43.2% of patients treated with PTX in the present study did not develop other diseases. In further studies, it will be interesting to ascertain the role of PTX in the incidence of such comorbidities. In addition, serum AST, TP and TBili levels exhibited slight progressive increases that were statistically significant but not clinically relevant. By contrast, PTX reduced ALT serum levels by ~12% after 20 years. These results can indicate good hepatic function or a reduction in inflammation without the disappearance of the disease. It is

noteworthy that the natural progression of cirrhosis did not cease in the present study; 4 patients continued in Child-Pugh class A (well-compensated disease), 24.3% of patients progressed to class B (significant functional compromise) and 64.8% of patients progressed to class C (decompensated disease) within a period of 20.6 years. However, PTX significantly delayed the progression of the disease with a more prolonged overall survival time compared with that estimated in the patients studied. Recently, we published encouraging results utilizing PTX to treat patients with fulminant C hepatitis, Hepatocellular carcinoma and Hepatitis C; we demonstrated that PTX has improved medical conditions and increased patient survival rates (47-49). These studies support our hypothesis of the potential benefits of PTX in treating compensated cirrhosis.

PTX is a methylxanthines derivative and is a less expensive drug with >30 years of clinical use in reducing blood viscosity and platelet aggregation. PTX possesses anti-inflammatory, antioxidant, antitumor and antifibrotic properties (50), and suppresses NF-κB activation, specifically suppressing proinflammatory gene transcription, preventing tumor necrosis factor (TNF)α, interleukin (IL)-6 and transforming growth factor (TGF)-β synthesis (35). Additionally, PTX inhibits cyclooxygenase activity and fibrosis. Elevated serum concentrations of proinflammatory cytokines, such as TNFα, IL-1β, IL-6, interferon-γ and TGF-β, contribute to liver cell necrosis and the fibrotic development of liver cirrhosis (51). Several reports have demonstrated that PTX inhibits TNFα (37,52-54). In addition, it has been shown that PTX can reduce the development of hepatorenal syndrome and improve the survival of patients with this disease (55). Oakley *et al* (56) reported that inhibition of the kinase/NF-κB pathway is sufficient to increase the rate at which activated HSCs undergo apoptosis both *in vitro* and *in vivo*, and it was concluded that drugs that inhibit this pathway have potential therapeutic benefits. Other reports in the literature support the observations of the present study in that it is well-known that PTX exhibits a protective effect against chemotherapy- and radiotherapy-induced fibrosis (57), and PTX is also well-known to possess antifibrotic effects (50,58). In addition, PTX inhibits the TGF-β/SMAD pathway, reducing fibroblast activity and inhibiting fibrosis (36). Furthermore, PTX is well-tolerated and effective as a treatment for NASH and is an effective option in the treatment of complications of advanced liver disease (59,60). Collectively, these data provide an alternative explanation for the effect of PTX on the increased life expectancy of patients with compensated liver cirrhosis. In addition, our previous research has indicated that PTX may be beneficial in managing fulminant hepatitis and hepatocarcinoma (41,48).

With the data available, it is impossible to identify the underlying effects of PTX in patients with cirrhosis; the only hypotheses that could be arrived at concern the proposed antioxidant, anti-inflammatory and antifibrotic effects. Notably, PTX did not cause severe adverse events or side effects; only eight patients (3%) who received a PTX + propranolol-based regimen showed nausea and vomiting, but the patients did not discontinue their medications. The present study demonstrated that PTX was well-tolerated in patients with cirrhosis for 20.6 years, and the data suggested that PTX may be a candidate for repurposing in compensated cirrhosis. The strength of the present study lies in that, to the best of our knowledge, there has been no other similar study. Nonetheless, one limitation of the present study is that it was conducted at a single hospital and included a small number of clinical records. Prospective studies are therefore needed to further validate PTX administration management in patients with cirrhosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MAJL and AEJP conceptualized and designed the study and reviewed the manuscript. ESD, MVG, ABH and JAGO developed the methodology for extracting and analyzing data. EOA and GHF acquired data and wrote, reviewed and edited the manuscript. ABC used software, carried out data analysis and edited the manuscript . MAJL and ABC confirm the authenticity of all raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Biomedical Research Ethic Committee of Valentín Gómez Farías General Hospital, Institute for Security and Social Services for State Workers (Zapopan, Jalisco, Mexico; approval no. ISSSTE/CEI/019/08).

Patient consent for publication

Because of the study's retrospective nature, the patient informed consent exemption was approved.

Competing interests

The authors declare that they have no competing interests.

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