Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis

Fátima Higuera-de la Tijera, Alfredo I Servín-Caamaño, Aurora E Serralde-Zúñiga, Javier Cruz-Herrera, Eduardo Pérez-Torres, Juan M Abdo-Francis, Francisco Salas-Gordillo, José L Pérez-Hernández

Fátima Higuera-de la Tijera, Eduardo Pérez-Torres, Juan M Abdo-Francis, Francisco Salas-Gordillo, José L Pérez-Hernández, Liver Clinic, Gastroenterology Department, Hospital General de México, Dr. Eduardo Liceaga, Mexico City 06720, Mexico

Alfredo I Servín-Caamaño, Javier Cruz-Herrera, Internal Medicine Department, Hospital General de México, Dr. Eduardo Liceaga, Mexico City 06720, Mexico

Aurora E Serralde-Zúñiga, Fundación Mexicana para la Salud A.C, Mexico City 06720, Mexico

Author contributions: Higuera-de la Tijera F designed the study, provided financial support though the “Angeles Espinosa Yglesias 2010” stimulus, supervised the study, reviewed the statistical methods and wrote the final manuscript; Servín-Caamaño AI and Serralde-Zúñiga AE contributed to the acquisition, analysis and interpretation of the data and wrote the manuscript; Cruz-Herrera J, Pérez-Torres E, Abdo-Francis JM and Salas-Gordillo F contributed to the acquisition of data and cared for the patients; Pérez-Hernández JL reviewed the statistical methods and wrote the final manuscript; all of the authors read and approved the final manuscript.

Supported by Fatima Higuera-de la Tijera through the “Angeles Espinosa Yglesias 2010” stimulus granted by the FUNSALUD AC, AMPARO Foundation and FUNDHEPA AC, Mexico.

Ethics approval: The study was reviewed and approved by the “Hospital General de México, Dr. Eduardo Liceaga” Institutional Review Board.

Clinical trial registration: This study is registered at http://clinicaltrials.gov. The registration identification number is NCT02161653.

Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict of interest: The authors have not conflict of interest to declare. None of the researchers involved in this study have received fees for serving as a speaker, consultant or as advisory board member for any organization.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at fatimahiguera@yahoo.com.mx. Consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low. No additional data are available.

Open access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Fátima Higuera-de la Tijera, MD, MSc, Liver Clinic, Gastroenterology Department, Hospital General de México, Dr. Eduardo Liceaga, Dr. Balmis 148, Mexico City 06720, Mexico. fatimahiguera@yahoo.com.mx

Telephone: +52-55-27892000

Received: November 28, 2014

Peer-review started: December 1, 2014

First decision: December 26, 2014

Revised: January 16, 2015

Accepted: February 12, 2015

Article in press: February 13, 2015

Published online: April 28, 2015

Abstract

AIM: To evaluate the impact of metadoxine (MTD) on the 3- and 6-mo survival of patients with severe alcoholic hepatitis (AH).

METHODS: This study was an open-label clinical trial, performed at the “Hospital General de México, Dr. Eduardo Liceaga”. We randomized 135 patients who met the criteria for severe AH into the following groups: 35 patients received prednisone (PDN) 40 mg/d, 35 patients received PDN+MTD 500 mg three times daily, 33 patients received pentoxifylline (PTX) 400 mg three times daily, and 32 patients received PTX+MTD 500 mg three times daily. The duration of the treatment for all of the groups was 30 d.

RESULTS: In the groups treated with the MTD, the
Severe alcoholic hepatitis (AH) has a high mortality rate despite its standard therapy. Some populations, such as Hispanics, have responded poorly to standard therapy and show a mortality rate similar to those treated with placebos, particularly in patients classified as Age-Bilirubin-International normalized ratio-Creatinine (ABIC) classes B and C. Therefore, it is important to search for new therapeutic options that are effective and safe.

Acute and chronic alcohol exposure is associated with high oxidative stress and liver injury mediated by acetaldehyde and reactive oxygen species (ROS) are responsible for activating redox-sensitive transcription factors, such as nuclear factor-kappa B (NF-κB), thereby maintaining a pro-inflammatory profile.

Metadoxine (MTD), an antioxidant, participates in the synthesis of glutathione (GSH) and inhibits hepatic steatosis. The preliminary findings in patients with severe AH have demonstrated that MTD in combination with glucocorticoids improves the survival rates at 30 and 90 d as well as the response to steroid therapy, according to the Lille score.

The aim of this study was to evaluate the impact of MTD added to standard therapy using prednisone (PDN) or pentoxifylline (PTX) compared with monotherapy on the 3- and 6-mo survival rates of patients with severe AH.
Manual of Mental Disorders, Fourth Edition (DSM-IV); a history of atopy or asthma; diabetes; obesity; pregnancy; hepatitis B or C virus infection; or tuberculosis were excluded from the study.

Patients with an intake of illicit drugs, herbal products, antioxidant supplements (multivitamins, S-adenosyl-L-methionine, MTD, silymarin), or previous treatment with steroids or PTX within the previous two years were excluded.

Patients without family support or without access to telephone communication were also excluded.

Pre-inclusion screening
We obtained written informed consent from all of the patients before they were enrolled in the study. On the day of admission, we performed a clinical history and collected peripheral blood samples to determine each patient's glucose, urea, creatinine, total bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, ALT, AST, sodium, potassium, albumin, leukocytes, neutrophils, hemoglobin, platelets, PT and international normalized ratio levels. The patients were also tested for HBsAg, anti-HBs, anti-HBc, IgM anti-HBc, with serological screening for the hepatitis C virus and human immunodeficiency virus. The screening for bacterial infections included urine, blood and ascites cultures, as well as chest radiography and a neutrophil count in ascites. A liver ultrasound and endoscopy were performed to determine the presence of varices in all of the patients.

Randomization and treatment groups
The patients were randomized into four treatment groups. For the randomization, we used the Epidat 3.1 statistical program (Galicia, Spain 2006) to construct a table of random numbers to compose four groups of equal size (Figure 1).

We evaluated 217 patients who met clinical and biochemical criteria for severe AH. However, 82 subjects met one or more exclusion criteria: 47 were diabetics, 12 had hepatitis C chronic infection, 8 consuming illicit drugs, 7 were previously treated with steroids, 3 previously with pentoxifylline, 3 did not sign consent form, 1 hepatocellular carcinoma, and 1 hepatitis B chronic infection.

Follow-up: 3 and 6 mo or until death if it occurred before this time. All patients were included in the intention to treat analysis.
daily); a group receiving PTX (at a dose of 400mg three times daily) and MTD (at a dose of 500 mg three times daily). In all cases, the duration of treatment was 30 d, or until death if it occurs earlier. The 500-mg metadoxine tablets (Abrixone®) were provided by Eurodrug Laboratories as a donation for our institution. The 40-mg prednisone tablets and the 400-mg pentoxifylline tablets provided by our institution. Eurodrug Laboratories provided comments regarding the study design but were not involved in the writing of the protocol, the conduct of the trial, the decision-making with respect to the trial, the analysis of the data, or the preparation of the manuscript. The doses were selected on the basis of previous studies[1,2,13]. The dose for metadoxine was selected on the basis of the study conducted by Caballería et al[13].

**Study phase and endpoints**
The primary endpoints were the 3- and 6-mo survival rates. The secondary endpoints were the development or progression of acute renal failure (ARF), variceal bleeding (VB), hepatic encephalopathy (HE), bacterial or fungal infections, adverse effects and a relapse to alcohol consumption between 30 d and 6 mo of the follow-up. We also performed a sub-analysis stratifying the patients according to their ABIC class.

The patients were monitored weekly during the first month, two times per month during the second and third months, and monthly thereafter until 6 mo. Each visit included a clinical examination and the collection of peripheral blood samples. During the first two weeks, all of the patients were hospitalized; subsequently, each investigator determined the duration of the hospitalization. For the hospitalized patients, the medications were administered under the supervision of physicians and nurses. For outpatients, adherence to treatment was monitored by a family member and reported in a control diary. To increase compliance with the medication regimen, the patients were required to return the empty blisters at each visit.

In patients who were suspected of developing an infection during the study, cultures and chest radiography were performed if necessary. In patients who developed odynophagia or dysphagia, an endoscopic study was performed to identify esophageal candidiasis; when suspicious lesions were observed, brushing and mycological examinations were performed.

**Management of complications**

**ARF:** This condition was defined according to the criteria of the *Acute Kidney Injury Network* as an abrupt reduction (48 h) in renal function characterized by an increase of 0.3 mg/dL in the serum creatinine compared with the baseline value. The patients who had a baseline value of serum creatinine $\geq 1.5$ mg/dL at the time of admission were considered to have ARF[14,15]. These patients were treated with intravascular volume expansion using an albumin infusion at 1 g/kg for 48 h. The patients who did not respond to this treatment were evaluated for hepatorenal syndrome (HRS) according to the *Ascites International Club* criteria and were treated with a vasopressor (terlipressin or norepinephrine) and intravascular volume expansion with albumin[16,17].

**HE:** This condition was defined clinically by both neuropsychiatric alterations and neuromuscular signs according to the West-Haven criteria[18]. Patients with an HE grade of I or II were treated orally with L-ornithine-L-aspartate. Patients with an HE grade of III or IV were treated intravenously with L-ornithine-L-aspartate. In patients for whom L-ornithine-L-aspartate was contraindicated, oral lactulose for HE grades I or II and lactulose enemas for HE grades III or IV were prescribed.

**VB:** This condition was defined by the presence of melena or hematemesis associated with gastroesophageal varices as determined by an endoscopy. These patients were treated with terlipressin or octreotide, and fresh frozen plasma and blood were transfused as necessary. An endoscopic band ligation for esophageal varices or cyanoacrylate injection for gastric varices was performed, and antibiotic prophylaxis was prescribed. Subsequently, the patients received a secondary prophylaxis[19].

**Spontaneous bacterial peritonitis:** This condition was defined and treated according to the most recent guidelines of the European Association for Study of Liver Diseases[17].

**Other infections:** Urinary tract infections were diagnosed in the patients having urinary symptoms that were associated with abnormal urinary examinations and urinary cultures, including a bacterial count greater than 100000 CFU. An antibiotic therapy was prescribed based on the results of the urinary cultures.

Pneumonia was diagnosed in the patients who developed a cough with expectoration and confirmation on the chest X-ray. Treatment was initiated with ceftriaxone and clarithromycin, after which the antibiotic therapy was adjusted depending on the sputum culture results.

When patients developed odynophagia or dysphagia, esophageal candidiasis was suspected. The diagnosis was confirmed through oral cavity examinations and an endoscopy indicating the presence of compatible lesions; brushing was performed for a mycological examination in all of the cases, and treatment with fluconazole 100 mg twice daily was prescribed.

Patients with diarrhea were evaluated by microscopic examinations of fresh stool and stool cultures. These patients were treated empirically with ciprofloxacin
Table 1  Baseline characteristics of the patients

| Characteristic                  | PDN (n = 35) | PDN+MTD (n = 35) | PTX (n = 33) | PTX+MTD (n = 32) | P value |
|--------------------------------|--------------|------------------|--------------|------------------|---------|
| Male, n (%)                    | 33 (94.3)    | 32 (94.4)        | 31 (93.9)    | 28 (87.5)        | 0.40    |
| Age, yr                        | 43.1 ± 9.5   | 43.4 ± 9.0       | 43.4 ± 9.9   | 44.4 ± 9.1       | 0.94    |
| Alcohol intake, g/d            | 313.7 ± 157.1| 328.9 ± 142.5    | 365.9 ± 196.2| 346.5 ± 173.6    | 0.61    |
| Child-Pugh                     | 12.4 ± 1.0   | 12.4 ± 0.9       | 12.6 ± 1.0   | 12.5 ± 1.0       | 0.82    |
| Maddrey’s modified discriminant function | 70.9 ± 25.6 | 67.3 ± 19.3      | 93.4 ± 84.7  | 78.3 ± 40.2      | 0.14    |
| MELD                           | 28 ± 4       | 29 ± 6           | 31 ± 9       | 31 ± 7           | 0.19    |
| ABIC                           | 8.199 ± 1.3  | 8.604 ± 2.9      | 8.673 ± 1.8  | 8.677 ± 1.6      | 0.97    |
| Urea, mg/dL, Log10             | 1.60 ± 0.34  | 1.64 ± 0.31      | 1.66 ± 0.32  | 1.64 ± 0.42      | 0.94    |
| Creatinine, mg/dL              | 1.5 ± 0.7    | 1.5 ± 0.8        | 1.7 ± 1.1    | 1.9 ± 1.5        | 0.21    |
| Sodium, mEq/L                  | 135.1 ± 5.8  | 1327.5 ± 58      | 130.9 ± 5.1  | 1317.4 ± 57      | 0.57    |
| Albumin, mg/dL                 | 1.9 ± 0.4    | 1.9 ± 0.5        | 1.8 ± 0.4    | 1.8 ± 0.5        | 0.89    |
| Total bilirubin, mg/dL         | 24.4 ± 10.5  | 24.5 ± 10.1      | 23.0 ± 9.5   | 25.9 ± 11.6      | 0.73    |
| Alkaline phosphatase, U/L Log10| 2.3 ± 0.2    | 2.3 ± 0.2        | 2.2 ± 0.2    | 2.4 ± 0.2        | 0.29    |
| Gamma-glutamyltransferase, U/L Log10 | 2.5 ± 0.3 | 2.4 ± 0.3        | 2.4 ± 0.4    | 2.4 ± 0.3        | 0.73    |
| Aspartate aminotransferase, U/L Log10 | 2.3 ± 0.2 | 2.3 ± 0.2        | 2.2 ± 0.2    | 2.2 ± 0.3        | 0.39    |
| Alanine aminotransferase, U/L Log10 | 1.7 ± 0.2 | 1.7 ± 0.2        | 1.7 ± 0.2    | 1.7 ± 0.4        | 0.28    |
| Leucocytes, cell/mm³            | 20.9 ± 8.0   | 18.5 ± 8.0       | 19.5 ± 9.0   | 19.2 ± 10.3      | 0.71    |
| Neutrophils, cell/mm³           | 16.2 ± 7.0   | 15.7 ± 7.5       | 16.6 ± 8.5   | 17.0 ± 9.9       | 0.92    |
| Hemoglobin, g/dL                | 11.6 ± 2.7   | 11.8 ± 2.5       | 10.9 ± 3.0   | 11.4 ± 2.4       | 0.52    |
| Platelets, cell/mm³             | 178.1 ± 119.5| 186.0 ± 113.6    | 182.8 ± 117.7| 153.0 ± 84.0     | 0.61    |
| Prothrombin time in seconds     | 22.0 ± 5.8   | 21.1 ± 3.6       | 27.6 ± 18.5  | 23.2 ± 8.8       | 0.06    |
| INR                            | 1.9 ± 0.5    | 1.8 ± 0.3        | 2.4 ± 1.9    | 2.0 ± 0.7        | 0.06    |
| Cirrhosis on liver ultrasound, n (%) | 25 (71.4) | 20 (57.1)        | 26 (78.8)    | 20 (62.5)        | 0.24    |

**Statistical analysis**

The statistical methods of this study were reviewed by Fátima Higuera-de la Tijera, MD, MSc. and José L. Pérez Hernández, MD, MSc. From the “Hospital General de México, Dr. Eduardo Liceaga”. The distribution of variables was analyzed; in cases of quantitative variables with a non-normal distribution base, a 10-logarithmic transformation was performed to normalize their distribution for the analysis using parametric tests. Descriptive statistics were used. The quantitative variables were expressed as the mean ± SD, and the qualitative variables were expressed as proportions and percentages. To compare the basal characteristics between the groups, a one-way ANOVA was performed for the quantitative variables. Tukey’s or Tamhane’s T2 tests were used according to the homogeneity of the variance for the post hoc tests, and a χ² test with Yates correction or Fisher’s exact test were used for the qualitative variables. To compare the primary and secondary endpoints between the groups, an analysis with an intention to treat (ITT) was conducted. The χ² test with a Yates correction, Fisher’s exact test or Student’s t-test was used when needed, based on the variable type. A survival analysis was performed using Kaplan-Meier curves to evaluate the 3- and 6-mo survival and to evaluate the alcohol intake relapse between 30 d and 6 mo of follow-up and compare it with the log-rank test. To identify the main risk factors associated with 6-mo mortality, a multivariate analysis using a Cox regression was conducted. SPSS version 18.0 (Chicago, IL, United States 2009) and Epidat 3.1 (Galicia, Spain 2006) were used to perform the statistical analyses. A two-sided P value of 0.05 was considered to be statistically significant.

**RESULTS**

The baseline characteristics of the patients are listed in Table 1. In the groups receiving MTD, the survival rate was significantly higher at 3 mo than in the groups not receiving MTD: PTX+MTD 19/32 (59.4%) vs PTX 11/33 (33.3%), P = 0.04; PDN+MTD 24/35 (68.6%) vs PDN 7/35 (20%), P = 0.0001 (Figure 2).

In the groups receiving the MTD, the survival rate was significantly higher at 6 mo than in the groups not receiving MTD: PTX+MTD 16/32 (50%) vs PTX 6/33 (18.2%), P = 0.01; PDN+MTD 17/35 (48.6%) vs PDN 7/35 (20%), P = 0.003; (Figure 3).

There was no difference in the survival rates between the PDN and PTX monotherapy groups at 3 and 6 mo. There was no difference in the survival rate between the PDN+MTD and PTX+MTD groups at 3 and 6 mo.

According to their ABIC class, 13 patients (9.6%) were classified as class A, 82 patients (60.7%) as class B, and 40 patients (29.6%) as class C. The global survival according to the ABIC class was 10 patients (76.9%) for class A, 42 patients (51.2%) for class B, and 9 patients (22.5%) for class C. We performed a sub-analysis stratifying patients according to their ABIC class according to the two different groups of...
treatment into the group of 67 patients who received concomitant therapy with MTD (MTD Group) and the group of 68 patients who did not receive MTD (the standard therapy or ST Group). The improvement in the survival in the MTD Group was observed primarily in the ABIC class B: the MTD Group 30/38 (78.9%) vs the ST Group 12/44 (27.3%), \( P = 0.0001 \). There were no significant differences between the treatment groups in either the ABIC class A or ABIC class C patients: the MTD Group 6/6 (100%) vs ST Group 4/7 (57.1%) \( P = 0.19 \), and the MTD Group 7/23 (30.4%) vs ST Group 2/17 (11.8%) \( P = 0.25 \), respectively.

Regarding the development of complications at 3 mo of follow-up, there was significantly less development of HE and HRS in the patients who received the concomitant therapy vs the patients who received the PDN alone. There was no difference between the PTX+MTD vs the PTX group. Neither were there any differences among the groups regarding the development of VB or infections (Table 2).

The occurrence of adverse effects was similar in all of the groups, principally consisting of epigastric burning, nausea and vomiting, due to which 12 patients dropped out of the study. The patients who dropped out included 4 patients in the PDN and MTD group, 3 patients in the PDN group, 2 patients in the PTX group, and 3 patients in the PTX and MTD group. These patients were included in the ITT analysis because we verified that they had received at least 80% of the treatment. Serious adverse effects were not reported in any of the groups.

**Maintenance of abstinence:** Seventy-nine of the patients survived after 30 d (the end of therapy), 54 (68.4%) of whom had maintained alcohol abstinence and 25 (31.6%) of whom had relapsed into alcohol intake at 6 mo of follow-up. When we compared the groups, the patients receiving MTD were better able to maintain abstinence than the patients who did not receive MTD; MTD Group 35/47 (74.5%) vs ST Group 19/32 (59.4%), \( P = 0.02 \).

In the multivariate analysis, a relapse in alcohol intake was the primary independent factor predicting mortality at 6 mo. Additionally, the coexistence of cirrhosis on the ultrasound was identified as a predictor factor that was associated with mortality at 6 mo. In this study, the quantity of the alcohol intake was not associated with the 6-mo mortality. On the other hand, the treatment with MTD was identified as a protective factor (Table 3).

**DISCUSSION**

The mortality rate in our patients was high despite the treatment with PDN or PTX. However, other studies in Mexican population have also shown a high mortality rate and a poor response to steroid therapy. In a cross-sectional study, Ruiz-Zavála A reported a failure to respond to corticosteroids, evidenced by a Lille score greater than 0.45 in 90% of the patients diagnosed with alcoholic hepatitis (a mean Lille score of 0.80 ± 0.18)\(^{[20]}\). Additionally, in a clinical trial in Mexican patients with severe AH that compared treatment with PTX vs treatment with PDN, the mortality rate at 30 d was high, at 46.6% vs 59.9%, respectively, and there was no difference between the groups (\( P = 0.30 \))\(^{[3]}\). If we compare the mortality rates according to the ABIC class, Mexican patients have a higher mortality rate than other populations despite the treatment with steroids or PTX. The survival rate in the Mexicans vs the Europeans according to their ABIC class was as follows: an ABIC class of A, 81% vs 100%; an ABIC class of B, 50% vs 70%; and an ABIC class of C, 13% vs 25%, respectively\(^{[4,5]}\). The quantity of the alcohol intake may be an explanation for the higher mortality observed in the Mexican population, as Altamirano et al\(^{[6]}\) demonstrated that the consumption of more than 120 g per day of alcohol is associated with greater
Table 2  Development of complications at the 3-mo follow-up (n %)

| Complication | PDN+MTD (n = 35) | PDN (n = 35) | PTX+MTD (n = 32) | PTX (n = 33) | P value* | HR (95%CI)† | P value* | HR (95%CI)† |
|--------------|------------------|--------------|------------------|--------------|---------|-------------|---------|-------------|
| HE           | 10 (28.6)        | 21 (60.0)    | 13 (40.6)        | 17 (51.5)    | 0.008†  | 0.2 (0.1-0.7) | 0.38    | 0.6 (0.2-1.7) |
| HRS          | 11 (31.4)        | 19 (54.3)    | 11 (34.4)        | 16 (48.5)    | 0.05†   | 0.3 (0.1-1.0) | 0.25    | 0.5 (0.2-1.5) |
| VB           | 10 (28.6)        | 13 (37.1)    | 11 (34.4)        | 14 (42.4)    | 0.44    | 0.6 (0.2-1.8) | 0.51    | 0.7 (0.2-1.9) |
| Infections   | 11 (31.4)        | 14 (40.0)    | 11 (34.4)        | 12 (36.4)    | 0.45    | 0.6 (0.2-1.8) | 0.87    | 0.9 (0.3-2.5) |
| None         | 24 (68.6)        | 21 (60)      | 21 (65.6)        | 21 (63.6)    |         |             |         |             |
| UTI          | 0 (0)            | 3 (8.6)      | 3 (9.4)          | 6 (18.25)    |         |             |         |             |
| SBP          | 2 (5.7)          | 2 (5.7)      | 3 (9.4)          | 3 (9.15)     |         |             |         |             |
| Pneumonia    | 9 (25.7)         | 7 (20)       | 1 (3.1)          | 1 (3.0)      |         |             |         |             |
| EC           | 0 (0)            | 1 (2.85)     | 3 (9.4)          | 1 (3.0)      |         |             |         |             |
| Diarrhea     | 0 (0)            | 1 (2.85)     | 1 (3.1)          | 1 (3.0)      |         |             |         |             |

*Significant difference (P < 0.05); †P value comparing the PDN vs the PDN+MTD groups; ‡HR and 95%CI comparing the PDN vs the PDN+MTD groups; †P value comparing the PTX vs the PTX+MTD groups; †HR and 95%CI comparing the PTX vs the PTX+MTD groups. EC: Esophageal candidiasis; HE: Hepatic encephalopathy; HR: Hazard ratio; HRS: Hepatorenal syndrome; PDN: Prednisone; PDN+MTD: Prednisone + metadoxine; PTX: Pentoxifylline; PTX+MTD: Pentoxifylline + metadoxine; SBP: Spontaneous bacterial peritonitis; UTI: Urinary tract infection; VB: Variceal bleeding.

Table 3  Multivariate analysis: predictors of mortality at 6 mo in patients with severe alcoholic hepatitis

| Variable                        | HR (95%CI) | P value |
|---------------------------------|------------|---------|
| Relapse in alcohol intake†      | 8.9 (3.9-20.2) | 0.0001  |
| Cirrhosis†                      | 2.3 (1.1-4.7)  | 0.02    |
| Treatment with metadoxine‡      | 0.3 (0.2-0.7)  | 0.005   |
| Quantity of alcohol intake (> 150 g/d) | 1.8 (0.4-7.7) | 0.45    |

†Risk factor; †Protective factor. HR: Hazard ratio; 95%CI: 95% confidence interval.

In our study, the mean alcohol intake was greater than 300 g per day. Moreover, Mexican-American males have a higher prevalence of alcoholic cirrhosis and a higher mortality rate compared with Caucasians[21].

Controversial results exist concerning whether steroids or PTX is superior in improving the survival of patients with severe AH. In our study, there was no difference in the survival between the PDN and the PTX groups. Neither was there a difference in the survival between the PDN+MTD and PTX+MTD groups. However, in 2009, De et al.[22] performed a randomized, double-blind, controlled clinical trial to compare the efficacy of PTX and prednisolone in the prevention of fatal HRS and thus included 1103 patients who were randomized to one of four groups: prednisolone + placebo, PTX + placebo, prednisolone + PTX, or a double placebo group. The investigators found that prednisolone, but not PTX, was associated with a lower risk of 28-d mortality. In contrast, the mortality rate in the group that received PTX was similar to the mortality rate of those who received the double placebo. Beyond 28 d, neither of the drugs was associated with a survival benefit, and infections were approximately twice as frequent in the prednisolone group.

Our study shows that treatment with MTD may have a protective role, as it improves 3- and 6-mo survival rates. MTD is the ion pair between pyridoxine and pyrrolidone carboxylate, the cyclic amide of glutamic acid that is responsible for the synthesis and catalysis of GSH[23]. Alcohol exposure is associated with high oxidative stress[6]. The oxidative pathway for metabolizing alcohol involves alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase, and both of these enzymatic reactions reduce nicotinamide dinucleotide (NAD) to its reduced form of NADH. An excess of NADH causes several metabolic disorders, including the inhibition of the Krebs cycle and fatty acid oxidation, which favors steatosis and hyperlipidemia[8]. Acetaldehyde participates in alcohol-mediated liver injury by causing cellular damage, inflammation, and fibrogenesis[7]; it promotes cell death by depleting the concentration of reduced GSH, inducing lipoperoxidation, and increasing the toxic effect of the free radicals. The ROS can oxidize and damage the DNA, proteins and unsaturated fatty acids, thereby altering cell function[6].

The oxidation of alcohol also occurs through cytochrome P450’s generation of ROS, such as hydrogen peroxide and superoxide ions. In particular, cytochrome P450 2E1 (CYP2E1) is increased several-fold and contributes to lipoperoxidation and liver injury. CYP2E1 also converts alcohol to acetaldehyde. The ROS are responsible for activating the redox-sensitive...
transcription factors, such as NF-κB, and maintaining a pro-inflammatory profile. Other cytochromes, such as CYP1A2 and CYP3A4, may also contribute to the metabolism of ethanol.

Several studies have demonstrated that MTD increases the metabolism and depuration of ethanol and acetaldehyde in the liver and plasma and prevents the damage caused by ethanol and acetaldehyde in both hepatocytes and hepatic stellate cells. MTD also restores the concentrations of NAD, GSH and adenosine triphosphate in the brain and liver and acts as an antioxidant because the ion-pair molecule is capable of dissociating into N-oxide, which acts as scavenger to trap the ROS and free radicals. MTD inhibits the synthesis of the fatty acid esters in the liver, reduces the hepatic content of the triglycerides and prevents the injuries associated with lipoperoxidation.

The global survival according to the ABIC class in our patients was similar to that reported by Altamirano et al. in a previous cohort of Mexican patients. The majority of our patients (60.7%) were categorized as ABIC class B. We believe that the greatest benefit that we observed using MTD therapy in the ABIC class B may have occurred because this group had the largest proportion of the patients compared with the ABIC classes A and C. However, further studies that include more patients who are categorized as ABIC classes A and C are needed to validate this assumption.

In regard to the development of complications, there was significantly less development of HRS in patients who had received PDN+MTD compared with those who received PDN alone at the 3-mo follow-up. Although there was no significant difference between PTX+MTD and PTX alone, 14.1% fewer patients in the group treated with PTX+MTD developed HRS compared with the patients who received PTX alone (34.4% vs 48.5%, respectively). In our study, MTD had a protective effect on renal function. Previous studies have shown that MTD decreases the formation of acetaldehyde macromolecular adducts in all targets of ethanol toxicity, including the brain, liver and kidneys. The effect in the kidneys is due to two mechanisms of action: the inhibition of adduct formation and the increased excretion rate of acetaldehyde.

The impaired renal function is closely associated with the elevation of inflammatory markers (tumor necrosis factor-α, interleukin-1β, and interleukin-6), leading to both an increase in markers of oxidative stress and a decreased in antioxidants. All of these mechanisms are involved in the pathophysiology of SAH and could be modulated by MTD therapy.

There was less development of HE in the patients receiving therapy with PDN+MTD compared with those who received PDN alone. Moreover, 10.9% fewer patients developed HE in the group treated with PTX+MTD compared with the patients who received PTX alone (51.5% vs 40.6%, respectively). In our study, MTD demonstrated a protective effect over the patients’ mental status. Pyrrolidone carboxylate is an intermediate in the γ-glutamyl cycle, which is an amino acid transport system into the cell through the cell membrane. Unlike glutamic acid, the uptake of pyrrolidone carboxylate by the central nervous system (CNS) is possible because it crosses the hematooencephalic barrier. In the CNS, it exerts a number of actions on the cognitive and memory functions that are affected by alcohol, and it is important and clinically relevant to restore those superior functions. Once hydrolyzed by oxoprolinase, the open glutamic acid becomes available for important metabolic processes. Its derivative, N-acetyl glutamate, which is released in the subsequent metabolic steps, plays an essential role in maintaining the nitrogen balance because it activates the carbamoyl-synthetase I, a key enzyme in the urea cycle. Furthermore, by reacting with oxaloacetate, an intermediate of the Kreb’s cycle, it participates in the biosynthesis of aspartate, an essential element in the urea cycle, which is therefore activated from two different entry points. In addition, glutamate may react with ammonia to form glutamine, thereby contributing to the elimination of toxic ammonia and to the nitrogen fixation by the organism.

In our study, a relapse in alcohol intake was the primary independent factor predicting mortality at 6 mo. Alcohol abstinence is considered to be the cornerstone of the management of AH. In the results from the STOPAH trial, a relapse in alcohol consumption had a deleterious effect; at 1 year, the patients who either did not reduce or who increased their alcohol consumption had a 3-fold risk for death compared with the patients who abstained (OR = 2.99; \( P < 0.001 \)). The patients who reduced their alcohol consumption but not below a safe level still had a more than a 2-fold risk for death at 1 year compared with the patients who abstained (OR = 2.28; \( P = 0.032 \)), as did the patients who reduced their alcohol consumption to below a safe level (OR = 2.17; \( P = 0.031 \)). Wang et al. demonstrated that alcohol abstinence ameliorates AH by decreasing the liver enzyme and fibrotic markers and improving hepatic steatosis. In our study, the therapy with MTD helped patients to maintain alcohol abstinence. This finding is similar to those reported by several studies that have demonstrated that MTD is an effective therapy for abstinence. Currently, disulfiram, naltrexone and acamprosate are approved for the treatment of alcoholic dependency; however, all of these medications are contraindicated in patients with severe liver disease, such as our patients. Patients who have recovered from an episode of severe alcoholic hepatitis must be supported in maintaining alcohol abstinence without risk or compromise to their liver function. Bono et al. found that alcoholic patients who received treatment with MTD achieved alcohol abstinence in a greater
proportion compared with those who did not receive it. More recently, an interesting retrospective analysis by Leggio et al.\(^4\) found that patients with ALD who were treated with MTD had a significant decrease in drinks per week and demonstrated an improvement in the AST/ALT ratio compared with those who did not receive it. The beneficial neurological effects of MTD therapy in patients with attention-deficit/hyperactivity disorder have been demonstrated in several studies conducted by Manor et al.\(^5\) In animal models, the effects of MTD on CNS have been studied. Ethanol and acetaldehyde increase the activity of dopamine neurons in the reward areas of the CNS, and these actions are associated with the rewarding and reinforcing properties of the ethanol. MTD may favor abstinence through its ability to metabolize and to clear ethanol and its metabolites from the organism, as well as through its direct effect on neurotransmitters such as gamma-aminobutyric acid, acetylcholine and dopamine, all of which are involved in the neurobiology of alcohol craving\(^6\).

In this study, the presence of cirrhosis on the ultrasound was identified as a predictive factor associated with 6-month mortality. In a study by Altamirano et al.,\(^3\) the degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria were independently associated with 90-day mortality.

In conclusion, MTD improves the 3- and 6-month survival in patients with severe AH, and it has a tendency to improve serious complications, such as HRS and HE, particularly when it is added to PDN. The greatest benefit of MTD therapy was observed in the ABIC class B patients. However, further studies including a greater sample size with a larger number of severe AH patients categorized as ABIC classes A and C are needed to demonstrate whether MTD also improves survival in these groups. This study reaffirms the knowledge that alcohol abstinence is a key factor for survival in severe AH patients and that MTD is a safe therapy that helps to achieve this objective.

**Innovations and breakthroughs**

In the current study, the authors found that metadoxine is an effective therapy for severe alcoholic hepatitis; the patients treated with metadoxine had better survival at 3 and 6 months compared with those treated with standard therapy with steroids or pentoxifylline. Furthermore, it is well known that alcohol abstinence is an important factor associated with long-term survival in these patients. In this study, the authors found that the patients who received metadoxine were more likely to maintain alcohol abstinence, and their greater abstinence may be related to the improvements in the 6-month survival in the patients treated with this drug.

**Applications**

The results of this study suggest that metadoxine could be used as an effective therapy for patients with severe alcoholic hepatitis, and the validated results of other previous studies have found that metadoxine is an effective therapy to achieve alcohol abstinence.

**Terminology**

Severe alcoholic hepatitis is a condition characterized by a rapid onset of jaundice in the absence of biliary tract obstruction, painful hepateomegaly and ascites, transaminases > 2 times above the normal values, an aspartate aminotransferase/alanine aminotransferase ratio ≥ 2, neutrophilia, a total bilirubin > 5 mg/dL, and a Maddrey’s discriminant function > 32 (calculated with the formula \[4.6 \times (\text{patient prothrombin time (PT)} - \text{control PT, in seconds}) + \text{total bilirubin in mg/dL},\]) which occurs in patients with a history of chronic and heavy alcohol intake. Metadoxine is the ion pair between pyridoxine and pyrrolidone carboxylate, the cyclic amid of glutamic acid, which is responsible for the synthesis and catalyzation of glutathione.

**Peers review**

This is an interesting study, focusing on a therapeutic area with largely unmet needs. This is a single-center open-label clinical trial comparing pentoxifylline, prednisone or metadoxine alone or in combination to assess their efficacy in severe alcoholic hepatitis. The results showed that the groups that received metadoxine achieved better survival. As in other studies, the maintenance of alcohol abstinence was the best predictor of survival. This study found that alcohol abstinence is an independent prognostic factor of the six-month mortality and that patients treated with metadoxine were more likely not to relapse into alcohol consumption. However, intervention did not prevent the complications associated with cirrhosis, which may be because the study was underpowered or that the effect of abstinence itself rather than the intervention was the main predictor for survival.

**REFERENCES**

1. Mathurin P, Mendenhall CL, Carrithers RL, Ramond MJ, Maddrey WC, Garstide P, Ruett B, Naveau S, Chaput JC, Poynard T. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002; 36: 480-487 [PMID: 11943418 DOI: 10.1016/S0168-8278(01)00289-6]

2. Parker R, Armstrong MJ, Corbett C, Rowe J, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013; 37: 845-854 [PMID: 23489011 DOI: 10.1111/apt.12279]

3. Garrido-Garcia JR, Sánchez-Hernández G, Melchor-López A, Elizalde-Barrera CI, Sánchez-Vargas L. Pentoxifilina versus esteroido en la sobrevivencia a corto plazo en hepatitis aguda alcohólica severa [Article in Spanish]. Med Int Mex 2012; 28: 227-233

4. Dominguez M, Rincón D, Abraldes JG, Miquel R, Colmenero J, Bellot P, García-Pagán JC, Fernández R, Moreno M, Bañares R, Arroyo V, Caballería J, Ginés P, Bataller R. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol 2008; 103: 2747-2756 [PMID: 18721242 DOI: 10.1111/j.1572-0241.2008.01040.x]

5. Altamirano J, Higuera-de la Tijera F, Duarte-Rojo A, Martinez-Vázquez MA, Abraldes JG, Herrera-Jiménez LE, Michelen J, Zapata L, Perez-Hernández J, Torre A, González-González JA, Cardenas A, Dominguez M, Arroyo V, Ginés P, Caballería J, Bataller R. The amount of alcohol consumption negatively impacts

**COMMENTS**

**Background**

Severe alcoholic hepatitis is a disease with a high mortality rate despite the use of standard therapy with steroids or pentoxifylline. Oxidative stress plays a key role in the physiopathology of alcoholic hepatitis and therefore represents a novel therapeutic target that must be investigated.

**Research frontiers**

Previous studies have demonstrated that metadoxine increases the metabolism and depuration of ethanol and acetaldehyde in the liver and the plasma and prevents the damage caused by ethanol and acetaldehyde in the hepatocytes and hepatic stellate cells. Metadoxine also acts as an antioxidant because its ion-pair molecule is capable of dissociating into N-oxide, which acts as scavenger to trap the reactive oxygen species and free radicals. Furthermore, metadoxine can prevent the steatosis and injury associated with lipoperoxidation. Metadoxine is a drug currently indicated for treating acute alcohol intoxication; several studies have also validated its use for treating alcohol dependence. However, until the current study, metadoxine had not been evaluated as a therapy for patients with severe alcoholic hepatitis.
short-term mortality in Mexican patients with alcoholic hepatitis. *J Am Gerontol 2011; 106: 1472-1480 [PMID: 21556041 DOI: 10.1038/jjag.2011.141]

6 Voicu CS, Perlmutter G, Naveau S. Mechanisms of the inflammatory reaction implicated in alcoholic hepatitis: 2011 update. *Clin Res Hepatol Gastroenterol 2011; 35: 465-474 [PMID: 21571602 DOI: 10.1016/j.clinre.2011.01.017]

7 Seth D, Haber PS, Syn WK, Diehl AM, Day CP. Pathogenesis of alcohol-induced liver disease: classical concepts and recent advances. *J Gastroenterol Hepatol 2011; 26: 1089-1105 [PMID: 21545524 DOI: 10.1111/j.1440-1644.2011.06576.x]

8 Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol 2004; 34: 9-19 [PMID: 15670660 DOI: 10.1046.alcohol.2004.07.008]

9 Válı I, Blázovics A, Fehér J. [The therapeutic effect of metadoxine on alcoholic and non-alcoholic steatohepatitis]. *Orv Hetil 2005; 146: 2409-2414 [PMID: 16398154]

10 Higuera-de la Tijera F, Servin-Caamaño AI, Cruz-Herrera J, Serralle-Zúñiga AE, Abdo-Francis JM, Gutiérrez-Reyes G, Pérez-Hernández JL. Treatment with metadoxine and its impact on early mortality in patients with severe alcoholic hepatitis. *Ann Hepatol 2014; 13: 343-352 [PMID: 24756009]

11 Theodossi A, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut 1982; 23: 75-79 [PMID: 7052399 DOI: 10.1136/gut.23.1.75]

12 Lucéy MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med 2009; 360: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]

13 Caballera J, Parés A, Bró C, Mercader J, García Plaza A, Caballera L, Clemente G, Rodrigo L, Rodrés J. Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-control trial. Spanish Group for the Study of Alcoholic Fatty Liver. *J Hepatol 1998; 28: 54-60 [PMID: 9537864]

14 Mehta RL, Kellum JA, Shah SV, Mellor J, Stanton L, Bowers M, Ryder P, Austin A, Díaz Martínez A, Villamil Salcedo V, Cruz Higuera-de la Tijera F. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *Trials 2013; 14: 262 [PMID: 23958271 DOI: 10.1186/1745-6215-14-262]

15 Addolorato G, Ancona C, Capristo E, Gashbarrini G. Metadoxine in the treatment of acute and chronic alcoholism: a review. *Int J Immunopharmacol 2003; 16: 207-214 [PMID: 14611722]

16 Calabrese V, Carlino S, Chinini C, De Bernardis E, Rizza V. Metadoxine modulates the absorption, metabolism and elimination kinetics of ethanol. *Riv Ital Alcol 1986; 5: 44-49

17 Díaz Martínez MC, Díaz Martínez A, Villamil Salcedo V, Cruz Fuentes C. Efficacy of metadoxine in the management of acute alcohol intoxication. *J Int Med Res 2002; 30: 44-51 [PMID: 11921498 DOI: 10.1177/0306041402030001017]

18 Gutiérrez-Ruiz MC, Díaz L, Correa A, Souza V, Hernández E, Gómez-Quiróz LE, Kershensonbich D. Metadoxine prevents damage produced by ethanol and acetaldheyde in hepatocyte and hepatic stellate cells in culture. *Pharmacol Res 2001; 43: 431-436 [PMID: 11712874 DOI: 10.1006/phrs.2001.0883]

19 Calabrese V, Calderone A, Ragusa N, Rizza V. Effects of Metadoxine on cellular status of glutathione and of enzymatic defence system following acute ethanol intoxication in rats. *Drugs Exp Clin Res 1996; 22: 17-24 [PMID: 8839633]

20 Felicioli R, Saracchi I, Flagiello AM, Bartoli C. Effects of pyridoxine-pyridoxal-carboxylate on hepatic and cerebral ATP levels in ethanol treated rats. *Int J Clin Pharmacol Ther J Toxicol 1980; 18: 277-280 [PMID: 7192694]

21 Baldacci M, Catalani R, Bartoli C, Mura U. Effects of pyridoxine-pyridoxal-carboxylate on hepatic adenosine triphosphate levels in rats. *Boll Soc Itol Biol Sperr 1982; 58: 1643-1649 [PMID: 7168788]

22 Calabrese V, de Bernardis E, Rizza V. [Metadoxine in the control of oxidative stress caused by acute and chronic ethanol poisoning]. *Boll Soc Itol Biol Sperr 1986; 62: 1357-1363 [PMID: 3828134]

23 Calabrese V, Randazzo G, Ragusa N, Rizza V. Long-term ethanol administration enhances age-dependent modulation of redox state in central and peripheral organs of rat: protection by metadoxine. *Drugs Exp Clin Res 1998; 24: 85-91 [PMID: 9675549]

24 Malhotra PS, Singh BR, Narotam B, Kaur KP. A study of metadoxine in alcoholic liver disease [Abstract]. *J Assoc Physicians India 2005; 53: 352-353

25 Vedrova NN, Gnezidilova Nlu. [Metadoxine in combined treatment of alcohol damage to the liver]. *Klin Med (Mosk) 2001; 79: 56-58 [PMID: 11496744]

26 Fehér J, Válı I, Blázovics A, Lengyel G. The Beneficial effect of metadoxine (pyridoxine-pyridoxal-carboxylate) in the treatment of fatty liver diseases. *CEMED 2009; 3: 65-76 [DOI: 10.1556/CED.3.2009.1.6]

27 Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. *World J Gastroenterol 2014; 20: 17756-17772 [PMID: 25548474 DOI: 10.3748/wjg.v20.i47.17756]

28 Thabriti HF, Meknassi D, Meknassi D, Masson S, McCune A, Patch D, Richardson P, Roderick P, Ryder S, Wright M, Thrusz M. Steroids or pentoxifylline for alcoholic hepatitis (STOPAH): study protocol for a randomised controlled trial. *Trials 2013; 14: 262 [PMID: 23958271 DOI: 10.1186/1745-6215-14-262]

29 Higuchi T, Fukushima Y, Yamamoto C, Yamaaki T, Okawa O, Ohnishi Y, Okada K, Soma M, Matsumoto K. The influence of uric acid on interleukin-1 beta and interleukin-1 receptor antagonist production by peripheral blood mononuclear cells. *Ther


Orlowski M, Meister A. The gamma-glutamyl cycle: a possible transport system for amino acids. Proc Natl Acad Sci USA 1970; 67: 1248-1255 [PMID: 5274454 DOI: 10.1073/pnas.67.3.1248]

Merrill AH, Henderson JM. Diseases associated with defects in vitamin B6 metabolism or utilization. Annu Rev Nutr 1987; 7: 137-156 [PMID: 3300730 DOI: 10.1146/annurev.nu.07.070187.001033]

Garau B, Fadda F, Melis F, Gelso E, Gessa GL. Metadoxine (pyrrolidone carboxylate of pyridoxine) antagonizes the locomotor-stimulatory effect of ethanol in mice. Alcohol Alcohol 1992; 27: 501-504 [PMID: 1476554]

Wang T, Zhu D, Xu X, Xu Y. The amelioration of AH by abstinence and the attenuation of oxidative stress. Hepatogastroenterology 2012; 59: 73-76 [PMID: 21940381 DOI: 10.5754/htg1259]

Leggio L, Kenna GA, Ferrulli A, Zywia WH, Caputo F, Swift RM, Addolorato G. Preliminary findings on the use of metadoxine for the treatment of alcohol dependence and alcoholic liver disease. Hum Psychopharmacol 2011; 26: 554-559 [PMID: 22095793 DOI: 10.1002/hup.1244]

Guerrini I, Gentili C, Nelli G, Guazzelli M. A follow up study on the efficacy of metadoxine in the treatment of alcohol dependence. Subst Abuse Treat Prev Policy 2006; I: 35 [PMID: 17176456 DOI: 10.1186/1747-597X-1-35]

Pár A. [Treatment of alcoholic liver diseases. Abstinence, nutritional support, drug therapy, liver transplantation]. Orv Hetil 2000; 141: 827-833 [PMID: 10817009]

Rizzo A, Breda A, Moretto F, Pace M, Dotta C, Gelso E, Sanzuol F, Tessani C. [Therapeutic use of metadoxine in chronic alcoholism. Double blind study of patients in a department of general medicine]. Clin Ter 1993; 142: 243-250 [PMID: 8482064]

Bono G, Sinforiani E, Merlo P, Belloni G, Soldati M, Gelso E. Alcoholic abstinence syndrome: short-term treatment with metadoxine. Int J Clin Pharmacol Res 1991; 11: 35-40 [PMID: 1678735]

Manor I, Ben-Hayun R, Aharon-Peretz J, Salomy D, Weizman A, Daniely Y, Megiddo D, Newcorn JH, Biederman J, Adler LA. A randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of extended-release metadoxine in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2012; 73: 1517-1523 [PMID: 23290324 DOI: 10.4088/JCP.12m07767]

Manor I, Newcorn JH, Faraone SV, Adler LA. Efficacy of metadoxine extended release in patients with predominantly inattentive subtype attention-deficit/hyperactivity disorder. Postgrad Med 2013; 125: 181-190 [PMID: 23933905 DOI: 10.3810/pgm.2013.07.2689]

Manor I, Rubin J, Daniely Y, Adler LA. Attention benefits after a single dose of metadoxine extended release in adults with predominantly inattentive ADHD. Postgrad Med 2014; 126: 7-16 [PMID: 25295645 DOI: 10.3810/pgm.2014.09.2795]

Altamirano J, Miquel R, Katoonizadeh A, Abraldes JG, Duarte-Rojo A, Louvet A, Augustin S, Mookerjee RP, Michelen J, Smyrk TC, Buob D, Leteurtre E, Rincón D, Ruiz P, García-Pagán JC, Guerrero-Márquez C, Jones PD, Barritt AS, Arroyo V, Bruquera M, Bañares R, Ginés P, Caballeria J, Roskams T, Nevens F, Jalan R, Mathurin P, Shah VH, Bataller R. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014; 146: 1231-9.e1-6 [PMID: 24440674 DOI: 10.1053/j.gastro.2014.01.018]

P- Reviewer: Fernandez-Rodriguez CM, Hauser G, Park YM
S- Editor: Qi Y
L- Editor: A
E- Editor: Zhang DN

Higuera-de la Tijera F et al. Metadoxine improves survival in alcoholic hepatitis
