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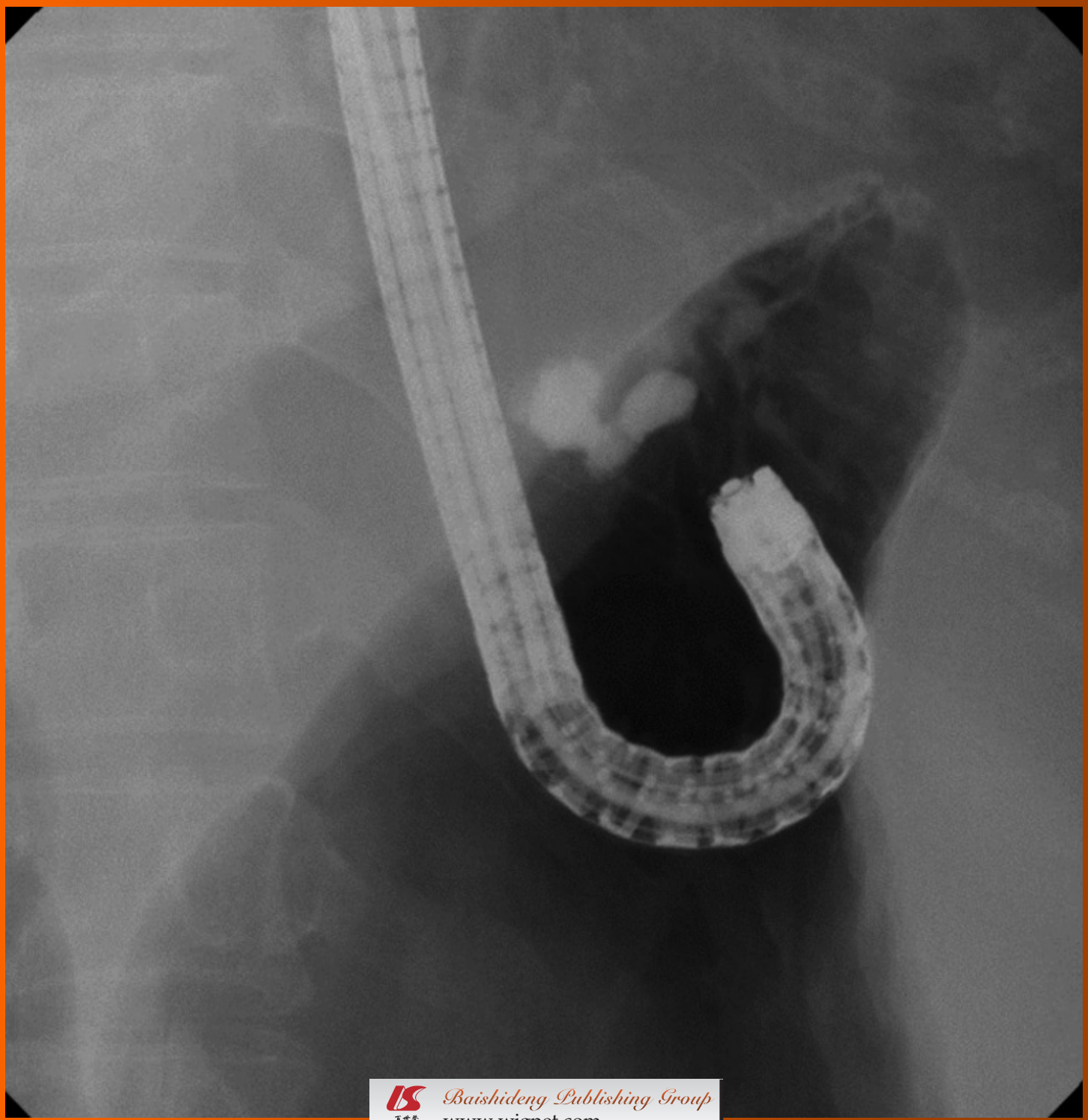

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Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
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Room 903, Building D, Ocean International Center,
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Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

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Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
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Fax: +852-3115-8812
Telephone: +852-5804-2046
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SUBSCRIPTION
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Room 903, Building D, Ocean International Center,
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Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

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EDITORIAL OFFICE
Shu-Jing Zhang, Assistant Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
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EDITORIAL

Budd-Chiari syndrome management: Lights and shadows

Andrea Mancuso

Andrea Mancuso, Epatologia e Gastroenterologia, Ospedale Niguarda Ca' Granda, Milano 20162, Italy
Author contributions: Mancuso A contributed solely to this work.
Correspondence to: Andrea Mancuso, MD, Epatologia e Gastroenterologia, Ospedale Niguarda Ca' Granda, Piazza Maggiore 3, Milano 20162, Italy. mancandrea@libero.it
Telephone: +39-2-64442111 Fax: +39-2-64442895
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Abstract

Budd-Chiari syndrome (BCS) is a rare disease whose management should follow a step by step strategy. Anticoagulation and medical therapy should be the first line treatment. Revascularization or TIPS are indicated in case of no response to medical therapy. OLT should be indicated as a rescue therapy and anticoagulation be started soon after OLT. However, no clear indication can actually be given about the timing of different treatments. Moreover, there is some concern about treatment of some subgroup of patients, especially regarding the risk of recurrence after liver transplantation. The topic of this paper is to critically review the actual knowledge of BCS management.

Key words: Budd-Chiari syndrome; Management; Liver transplantation

Peer reviewer: Hitoshi Maruyama, MD, Department of Medicine and Clinical Oncology, Chiba University Graduate School of Medicine, 1-8-1, Inohana, Chuou-ku, Chiba, 260-8670, Japan

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TIMING OF TREATMENT

It is widely accepted that the management of Budd-Chiari syndrome (BCS) should follow a step by step strategy. In fact, recently published guidelines suggest medical therapy (anticoagulation, treatment of underlying disease, symptomatic therapy of portal hypertension complications) as the first-line treatment, angioplasty/stenting the second-line (in patients with short-length stenoses not responding to medical therapy), TIPS the next step (in patients not responding to medical therapy and in case of no response to, or stenoses unsuitable for, angioplasty/stenting) and liver transplantation (LT) as the last chance when TIPS is not effective. However, as emphasized by the authors, the definition for response to therapy was not stated[1].

A recent proposal of the definition for response to BCS treatment has been published, as described in Table 1. The response was defined as *Complete* when there was no ascites, Na and creatinine were normal with no or low-dose diuretics (spironolactone 75 mg or furosemide 40 mg/die), there was a Factor V increase > 40% of the normal range, a bilirubin decrease < 15 mmol/L, no portal hypertension bleeding or spontaneous bacterial peritonitis and BMI was > 20 Kg/m^2. The response was defined as *Ongoing* when ascites was detectable but responsive to low-dose diuretics, Na and creatinine were normal, Factor V was increasing (if initially low) and bilirubin decreasing (if initially high). *Treatment Failure* was defined when criteria for complete or ongoing response were lacking. Following this strategy, 51 consecutive BCS patients were treated, obtaining a 5-year survival of 89%[2]. However, this proposal of a definition remains the only one actually published, reflects the experience of a single group and surely needs validation[1]. Moreover, it has to be stated if considering a treatment failure when the progression of liver disease is evident but outside the above definition, like in the case of histological progression (severe fibrosis/cirrhosis) or of worsening portal hypertension (new appearance or increasing size of esophago-gastric varices). Furthermore, to better understand

Table 1 Definition for response to Budd-Chiari syndrome treatment[2]

Complete response	No ascites
	Normal Na and creatinine with no or low-dose diuretics (spironolactone 75 mg or furosemide 40 mg/die)
	Factor V increase > 40% of the normal range
	Bilirubin decrease < 15 μmol/L
	No portal hypertension bleeding
	No spontaneous bacterial peritonitis
	Body mass index > 20 kg/m^2
Ongoing response	Ascites detectable but responsive to low-dose diuretics
	Normal Na and creatinine
	Factor V increase (if initially low)
	Bilirubin decrease
Treatment failure	When criteria for complete or ongoing response were lacking

the correct timing of therapy in BCS management, the efficacy of each treatment should be observed in a larger number of patients and be durable during follow up.

The outcome of BCS with currently available treatment is described in a recently published prospective multi-center study in which 163 BCS patients were followed for a median of 17 mo (range 1-31 mo); 18% had also portal vein thrombosis, 84% had a thrombophilic syndrome, 46% of which a myeloproliferative disorder (MPD). Overall, 29 died [8 liver failure, 2 multiple organ failure (MOF), 2 bleeding]. The 24 mo survival was 82% (24 mo LT Free Survival 68%). Prognostic factors were sex (male), ascites and creatinine. Importantly, about 1/3 of the patients remained on medical therapy only[3]. However, the follow-up was not long enough to eventually show the consequences of a slowly progressing disease, possibly prevented by early recanalization/decompression, and to draw any definitive conclusion about the exact timing of treatment. Furthermore, we wonder if early decompression could stop or reverse histological progression of hepatic disease, finally improving long-term outcome.

RECANALIZATION OR DECOMPRESSION OF BUDD-CHIARI SYNDROME

In the case or short-length stenoses, angioplasty/stenting is a therapeutical approach suitable for BCS with a good medium term outcome in some experience[4-6]. However, no data can argue against the use of TIPS also in the subgroup of patients with short-length stenoses since a prospective comparison between TIPS and angioplasty/stenting has not been performed, to our knowledge. Such a therapeutical choice in this subgroup of patients should be based on local expertise.

TIPS is surely the mostly used treatment for BCS when medical therapy fails[2,3]. In early experiences, TIPS has proved effective as BCS treatment[7-9]. Moreover, TIPS can be successful also in the technically difficult case of extension of thrombosis to the portal vein tree[10,11]. Recently, a multi-center study provided long-term data on TIPS treatment for 147 BCS patients not responding to medical treatment or recanalization. TIPS was successful in 124 BCS patients, who were followed for a median of 36.7 mo. Overall, 16 (13%) died, 8 (6.5%) underwent OLT. Main complications were hepatic encephalopathy in 21% and TIPS dysfunction in 41% (significantly less in PTFE-covered than in Bare stents). The 10-year survival was 69%. Prognostic factors were age, bilirubin and INR[12].

LIVER TRANSPLANTATION FOR BUDD-CHIARI SYNDROME

LT is the last chance for BCS syndrome non responsive to either medical therapy or recanalization/decompression[1,13-16]. A European multi-center study reported long-term data on 248 patients who underwent LT for BCS between 1988 and 1999. MPD was the underlying syndrome in 45%. LT was performed electively in 55%, in emergency in 21%. Hepatic celluler cancer was incidentally found in explanted liver in 3. Before LT, 19% had portal vein thrombosis and 16% Inferior vena cava thrombosis. Median follow-up was 48 mo. Overall, 67 (27%) died (49% in the first month). Causes of death were sepsis in 47%, graft dysfunction or hepatic artery thrombosis in 19%, venous thrombosis in 12%, cardiac in 9% and brain damage in 5%. There was a significantly increased mortality if LT was shortly after SPSS or TIPS. Thirty-seven patients underwent re-LT (4 twice). The 10-year survival was 68%. After 1 year there were 9 deaths, seven of which were in MPD patients. Causes were: 4 BCS recurrence, 1 leukaemia (7 years post-LT), 1 ovarian cancer, 1 colangitis, 2 not known. Anticoagulation after LT was performed by 200/235 (18 heparin or aspirin), suspended in 10, all of which were believed to have a cause of BCS reversible after LT (antithrombin Ⅲ and Protein C deficiency); all had an uneventful outcome but one who reported pulmonary embolization 1 year after, when anti-phospholipid syndrome was discovered. Complications post-OLT in the patients treated with anticoagulation were thrombosis in 27 (11%), 11 of whom (41%) died; recurrence of BCS in 6 (1 Re-OLT, 1 TIPS, 4 death); bleeding in 27 (11%), 2 of whom died (intracranial bleeding). Prognostic Factors were pre-OLT renal function and pre-OLT SPSS/TIPS[17]. However, the

prognostic factor of a previous shunt before LT has to be weighed cautiously because it can only reflect the fact that patients who underwent TIPS before LT had the most severe liver disease. Moreover, a recent American multi-center study found no negative effect of TIPS on the following LT outcome[18]. Finally, recent data show promising results of living donor LT for BCS[19].

The possibility of BCS underlying disease progression is a concern, in particular the development of leukaemia in MPD after LT. Preliminary multi-center studies failed to draw conclusions on this topic, given that long-term outcome was not correlated to the type of underlying disease predisposing to BCS[10,11]. However, although not statistically significant, 7 of the 9 patients who died after 1 year post LT in the European study had MPD[10]. The impact of Jak2 and MPL mutations on prognosis of splanchnic vein thrombosis (either BCS or portal vein thrombosis) was recently reported in 241 cases. In BCS, patients with the Jak2V617F mutation had a significantly more severe disease (Child-Pugh, Clichy PI, Rotterdam score). Moreover, event free survival tended to be decreased, but not significantly, in patients with Jak2V617F mutation and significantly decreased in MPD. However, at a median follow up of 3.9 years, overall survival was not influenced by either Jak2V617F mutation or MPD[20].

CONCLUSION

BCS should be treated following a step by step strategy. Anticoagulation and medical therapy should be the first line treatment. Revascularization or TIPS are indicated in case of no response to medical therapy. OLT should be indicated as a rescue therapy and anticoagulation be started soon after OLT. However, given that accepted criteria of response to therapy is still lacking, the timing of treatment, in particular TIPS, should be re-evaluated in future, well-designed multi-center studies.

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EDITORIAL

Role of ezetimibe in non-alcoholic fatty liver disease

Theodosios D Filippatos, Moses S Elisaf

Theodosios D Filippatos, Moses S Elisaf, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece
Author contributions: Filippatos TD prepared and wrote the editorial; Elisaf MS made corrections and did the final editing of the manuscript.
Correspondence to: Moses S Elisaf, MD, FRSH, FASAA, Professor of Medicine, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece. egepi@cc.uoi.gr
Telephone: +30-2651-7509 Fax: +30-2651-7016
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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and inflammatory changes. Ezetimibe inhibits cholesterol absorption from the intestinal lumen into enterocytes. The molecular target of ezetimibe is the sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1). Human NPC1L1 is abundantly expressed in the liver and may facilitate the hepatic accumulation of cholesterol. Ezetimibe exerts beneficial effects on several metabolic variables. Ezetimibe treatment attenuates hepatic steatosis and is beneficial in terms of NAFLD biochemical markers. The combination of ezetimibe with other interventions may also be beneficial in NAFLD patients. Our group investigated the ezetimibe-orlistat combination treatment in overweight and obese patients with hypercholesterolemia, with beneficial effects on NAFLD biochemical markers. These results are promising for patients with NAFLD, who usually have increased cardiovascular disease risk and need a multifactorial treatment. However, it should be mentioned that most results are from animal studies and, although modest elevation of liver function tests may raise the suspicion of NAFLD, none of these tests are sensitive to establish the diagnosis of NAFLD with great accuracy.

Key words: Ezetimibe; Non-alcoholic fatty liver disease; Hypolipidemic treatment; Insulin resistance; Acarbose; Orlistat

Peer reviewers: Ignazio Grattagliano, MD, General and Internal Medicine, University of Bari, P.zza G. Cesare, 111, 70043 Bari, Italy; Wing-Kin Syn, MD, Hepatologist, 1GI Division, Duke University, Suite 1073, 595 LaSalle Street, Durham, NC 27710, United States

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries. NAFLD encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and inflammatory changes[1,2]. Furthermore, NAFLD is associated with peripheral and hepatic insulin resistance and many of the features defining the metabolic syndrome[3,4]. Furthermore, it was shown that being overweight and obese may result to fibrotic and inflammatory hepatic injury, an effect mediated in part by insulin resistance[5].

ROLE OF EZETIMIBE IN NAFLD

Ezetimibe belongs to a class of hypolipidemic agents, the cholesterol absorption inhibitors, which inhibit cholesterol absorption from the intestinal lumen into enterocytes[6]. The molecular target of ezetimibe is the sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1)[7,8]. Besides its low-density lipoprotein cholesterol (LDL-C) lowering effect, ezetimibe exerts beneficial effects on several other

metabolic variables[9]. Of interest, human NPC1L1 is also abundantly expressed in the liver and may facilitate the hepatic accumulation of cholesterol[10].

Ezetimibe treatment appears to attenuate hepatic steatosis[11]. Jia *et al*[12] fed NPC1L1 knockout (L1-KO) mice and their wild-type controls for 24 wk with a high-fat diet and found that a high-fat diet did not cause fatty liver. L1-KO mice were completely protected against high-fat diet-induced hyperinsulinemia under both fed and fasted states and during glucose challenge. Furthermore, hepatic fatty acid synthesis and levels of mRNAs for lipogenic genes were substantially reduced in L1-KO mice[12]. Inhibition of NPC1L1 by ezetimibe in Zucker Obese Fatty rats improved hepatic insulin signaling as well as hepatic steatosis[13]. Hence, NPC1L1 contributes to hepatic insulin resistance through cholesterol accumulation and its inhibition could be a potential therapeutic target of hepatic insulin resistance[13].

Ezetimibe administration in humans has also been beneficial in terms of NAFLD biochemical markers[14], including fatty acid concentration[15]. In a study, long-term ezetimibe treatment (24 mo) was given in 45 patients with newly diagnosed liver biopsy-proven NAFLD (Table 1)[16]. Ezetimibe significantly improved visceral fat area [from (155.9 ± 38.9) to (146.5 ± 34.8) cm^2, $P < 0.05$), fasting insulin [from (10.9 ± 5.6) to (9.4 ± 5.1) mU/L, $P < 0.05$], homeostasis model assessment [HOMA, from (3.04 ± 1.17) to (2.62 ± 1.24), $P < 0.05$], the concentration of triglycerides [from (168 ± 94) to (138 ± 88) mg/dL, $P < 0.05$], total cholesterol [from (228 ± 44) to (194 ± 36) mg/dL, $P < 0.01$), LDL-C [from (136 ± 33) to (114 ± 31) mg/dL, $P < 0.05$), as well as the mean levels of small LDL and very small LDL [from (37.9 ± 5.4) to (33.2 ± 5.1) mg/dL, $P < 0.05$ and from (23.8 ± 4.8) to (18.6 ± 2.8) mg/dL, $P < 0.01$, respectively]. Ezetimibe also significantly lowered serum alanine aminotransferase [ALT, from (62 ± 25) to (49 ± 23) IU/L, $P < 0.01$] and high-sensitivity C-reactive protein [hsCRP, from (883 ± 408) to (685 ± 377) μg/L, $P < 0.05$] levels. The histological features of steatosis grade ($P = 0.0003$), necroinflammatory grade ($P = 0.0456$), ballooning score ($P = 0.0253$) and NAFLD activity score ($P = 0.0007$) were significantly improved compared with baseline.

ROLE OF DRUG COMBINATIONS INCLUDING EZETIMIBE IN NAFLD

Ezetimibe in the setting of hyperlipidemia is usually given combined with other hypolipidemic drugs[6], which leads to complementary results in terms of cardiovascular disease risk factors due to the different mechanisms of action. The combination of ezetimibe with other interventions seems to be beneficial in NAFLD patients. For example, compared with weight loss alone, the administration of ezetimibe plus weight loss in 25 obese subjects significantly decreased intrahepatic triglyceride content (-18%), as well as plasma hsCRP (-53%), interleukin-6 (-24%), LDL-C (-18%), and campesterol (-59%) concentration (all $P < 0.05$)[17]. Furthermore, combined treatment of ezetimibe with insulin-sensitizing agents had greater effect on hepatic fat content and lipid peroxidation compared to monotherapy in the methionine choline-deficient diet rat model of NAFLD[18]. Interestingly, the combination of ezetimibe and acarbose for 24 wk reduced steatosis, inflammation and fibrosis in the liver, compared with long-term monotherapy with either drug, in a high-fat diet-induced NAFLD mouse model (C57BL/6J mice)[19]. The combination treatment also significantly increased the expression of microsomal triglyceride transfer protein and peroxisome proliferators-activated receptor-alpha1 in the liver, compared with either monotherapy.

Table 1 Effects of ezetimibe, alone or combined with other drugs, in non-alcoholic fatty liver disease-related variables in humans

Drug (s)	Parameter
Ezetimibe[16]	↓Visceral fat area ↓HOMA ↓Triglycerides, ↓total cholesterol, ↓LDL-C ↓ALT ↓hsCRP ↓Steatosis grade and NAFLD activity score
Ezetimibe plus weight loss[17]	↓Intrahepatic triglyceride content ↓hsCRP ↓Interleukin-6 ↓LDL-C
Ezetimibe plus orlistat[20-22]	↓Body mass index and waist circumference ↓Total cholesterol and triglycerides ↓HOMA ↓ALT, AST, γGT

NAFLD: Non-alcoholic fatty liver disease; HOMA: Homeostasis model assessment; LDL-C: Low density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γGT: γ-glutamyl-transpeptidase; hsCRP: High sensitivity C-reactive protein.

Our group investigated the ezetimibe-orlistat combination treatment in 88 overweight and obese patients with hypercholesterolemia, who were randomised to ezetimibe (group E), orlistat (group O) and their combination (group OE)[20-22]. We observed significant within-group changes in body mass index, waist circumference and body weight, which were significantly greater in groups receiving orlistat. We also observed significantly greater reductions in total cholesterol, triglycerides and apolipoprotein B levels in the combination group compared with monotherapy groups. Parameters of carbohydrate metabolism were significantly improved in groups receiving orlistat (i.e. in groups that lost weight) compared with the ezetimibe group. The activities of ALT (-16% in group O, -18% in group E, -14% on group OE, all $P < 0.05$) and gamma-glutamyl-transpeptidase (gGT, -15% in group O, -11% in group E, -25% in group OE, all $P < 0.05$) were improved in all treatment groups, whereas aspartate aminotransferase activity improved only in the combination group (-17%, $P < 0.05$).

CONCLUSION

These results are promising for patients with NAFLD, who usually have increased cardiovascular disease risk and need a multifactorial treatment. However, it should be mentioned that, although modest elevation of liver function tests may raise the suspicion of NAFLD, none of these tests are sensitive to establish the diagnosis of NAFLD with great accuracy[23]. Minimal requirement of any form of NAFLD resolution should be a lower fibrosis score. Furthermore, most results are given by animal studies which do not always correspond to human physiology.

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CASE REPORT

Bee sting therapy-induced hepatotoxicity: A case report

Adel Nazmi Alqutub, Ibrahim Masoodi, Khalid Alsayari, Ahmed Alomair

Adel Nazmi Alqutub, Ibrahim Masoodi, Khalid Alsayari, Ahmed Alomair, Division of Gastroenterology and Hepatology, King Fahad Medical City, Riyadh 11525, Saudi Arabia

Author contributions: Alqutub AN helped with the preparation of the manuscript and the patient presented to him with progressive jaundice; Masoodi I designed the report, wrote the discussion portion and edited the whole paper; Alsayari K helped in the preparation of the clinical history portion of the report; Alomair A helped with the introductory portion of the paper and revised the manuscript.

Correspondence to: Ibrahim Masoodi, MD, DM (Gastroenterology) FACP, Division of Gastroenterology, King Fahad Medical City, Riyadh 11525, Saudi Arabia. ibrahimmasoodi@yahoo.co.in

Telephone: +966-1-12889999-1244 Fax: +966-1-12889999-1245
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Abstract

The use of bee venom as a therapeutic agent for the relief of joint pains dates back to Hippocrates, and references to the treatment can be found in ancient Egyptian and Greek medical writings as well. Also known as apitherapy, the technique is widely used in Eastern Europe, Asia, and South America. The beneficial effects of bee stings can be attributed to mellitinin, an anti-inflammatory agent, known to be hundred times stronger than cortisone. Unfortunately, certain substances in the bee venom trigger allergic reactions which can be life threatening in a sensitized individual. Multiple stings are known to cause hemolysis, kidney injury, hepatotoxicity and myocardial infarction. The toxicity can be immediate or can manifest itself only weeks after the exposure. We describe hepatotoxicity in a 35-year-old female, following bee sting therapy for multiple sclerosis. She presented to our clinic 3 wk after therapy with a history of progressive jaundice. The patient subsequently improved, and has been attending our clinic now for the last 9 mo.

Key words: Bee sting therapy; Hepatotoxicity; Mellitinin; Prothombotic state

Peer reviewers: Neil Louis Julie, MD, Gastroenterology and Hepatology, 7609 Exeter Rd, Bethesda, MD 20814, United States; Agustin Castiella, MD, Gastroenterology and Hepatology Unit, Hospital Mendaro, Mendaro, 20850, Spain

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INTRODUCTION

Bee venom therapy is the specialized form of apitherapy, and requires the expertise of a trained practitioner. Usually, a course of treatment starts with testing the patient for allergy, which is known to occur in 1% of the general population. Bee venom is administered in the form of a direct bee sting or else by injection of a venom extract. The treatment is usually given twice a week. Some reports have shown beneficial effects of bee venom in postherpetic neuralgia[1], swine flu[2], fibromyalgia and multiple sclerosis, *etc.*, while other reports have described severe toxicities developing in response to bee venom therapy[3,4]. Animal models have been used to study the toxicity caused by bee stings. Bee stings cause hemoconcentration which might be related to the marked edema induced by the venom. Following bee stings there is an increase in various cytokines like interleukin (IL)-1β, IL-6, tumor necrosis factor-α, *etc.* In a mouse model using the subcutaneous route, rapid increases in serum alanine aminotransferase and aspartate aminotransferase transaminases, creatinine, urea nitrogen, uric acid, sodium and chloride electrolytes, and creatine kinase were recorded, indicating damage to liver, kidneys, and skeletal muscle[5]. We describe hepatotoxicity following apitherapy in a young female in this brief report.

CASE REPORT

A 35-year-old female presented to our clinic with a history of progressive jaundice of 3 wk duration. She denied history of abdominal pain, fever, viral prodrome or offending drug intake. She was an established case of multiple sclerosis of 10 years duration, in remission (fully ambulatory without any neuro-deficit) for the last 5 years. She had received apitherapy 5 years back and had developed a similar illness; however, she was not evaluated at that time. This year, 10 bees were put on her legs and arms by a local practioner. She described lot of fatigue soon after therapy but remained hemodynamically stable. Several days later she developed anorexia, and noticed that her urine was highly colored; attendants noticed yellowish discoloration of her sclera. She was brought to our clinic showing these symptoms. She denied any melena or bleeding or loss of consciousness. On examination she was conscious, oriented, deeply icteric, with no lymph adenopathy. She had no pedal edema and there were no petechial spots. Her systemic examination was unremarkable. She had normal liver span and there was no ascites. On evaluation she had hemoglobin of 130 g/L with a normal cell count and platelet count. Her liver function test results are shown in Figure 1. There was predominantly direct hyper bilirubinemia, serum Bilirubin was 637 μmol, serum glutamic-oxaloacetic trensaminase (SGPT) and serum alanine aminotransferase (AST) and alkaline phosphatase levels were also elevated (normal range < 39 IU/L) as shown in Figure 1. An ultrasound examination of her abdomen revealed a liver of normal size and echo texture with normal intra hepatic veins. She had a normal common bile duct diameter and no intra-hepatic bile duct dilatation. Her kidney function tests were normal. Her viral markers (HBsAg, IgM HEV, IgM HAV, and Anti HCV) were all negative. Her serum cerulo plasmin levels, iron profile and thyroid stimulating hormone levels were all within normal limits. She had no features of hemolysis and her celiac profile was negative. However, her antinuclear antibodies (ANA) levels were positive (1:640) with high IgG titers (IgG1 13.20 g/L) on the day of presentation. Anti mitochondrial antibody and anti smooth muscle antibody titers were also elevated. She was managed with capsule ursodeoxycholic acid 500 mg orally twice daily for a period of 8 wk, and her liver function tests were serially followed. She showed a progressive clinical improvement. Her liver function tests normalized over a period of 8 wk (Figure 1). She had no coagulopathy or altered sensorium during her whole illness. She is clinically fine and has been regularly attending our clinic for the last 9 mo. On follow-up, all her autoimmune markers became negative after 8 wk.

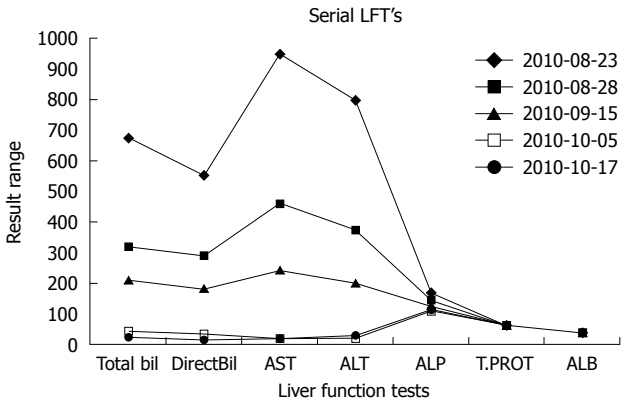

Figure 1 Serial liver function tests of the index case. AST: Aspartate aminotransferase (IU); ALT: Alanine aminotransferase (IU); ALP: Alkaline phosphatase (IU); ALB: Albumin (gm/dL); T.PROT: Total protein (gm/dL); Bil: Bilirubin (μmol).

DISCUSSION

The index case had a temporal profile suggestive of liver cell damage following bee sting therapy. She was extremely tired after therapy; however, she had no anaphylaxis or renal failure. She started showing symptoms of clinical jaundice 3 wk after the therapy, but maintained her sensorium and the synthetic parameters of liver cell function. The liver cell injury was self-limiting, with a complete improvement in her biochemical profile over a period of 8 wk. The spectrum of bee sting toxicity is variable. Some patients can develop life-threatening anaphylaxis but most of the patients simply develop local pain and reaction. Reports of renal, cardiac and liver toxicities following multiple bee stings have been described in the literature. Lim *et al*[6] described the biochemical profiles in a series of 17 patients with bee stings. The authors observed that out of 17 patients, an elevation of liver enzymes was seen in 50% (9/17). Authors in the same study observed an elevation of serum creatine phosphokinase and serum lactate dehydrogenase levels, which correlated with muscle damage on histology. All patients in their series had transient elevations of liver enzymes and had no sequelae like that of the index case. In an animal model, Neuman *et al*[7] observed that the hepatotoxicity associated with venom sac extract was proportional to the dose of toxin used, and that liver cell damage due to venom was of the cholangiocellular type. The authors were of the opinion that no further biochemical proof is needed to establish the hepatotoxicity of venom sac extract. Bee stings activate mast cells and trigger a prothrombotic state. Mast cell activation followed by acute coronary syndrome was described by Mytas *et al*[4] in a 58-year-old man with no history of cardiac disease, who had been stung by bees. In their case, the patient's coronary angiography showed left anterior descending artery thrombotic lesion. In a similar setting, a significant thrombotic lesion in the right coronary artery was demonstrated by Murat *et al*[8], reflecting prothrombotic phenomenon after a bee sting. The prothrombotic state is not restricted to coronaries only; Temizoz *et al*[9] reported focal neurological deficit 2 h after being stung by a bee in a 60-year-old male, and magnetic resonance imaging of his brain demonstrated cerebral infarction. It is quite possible that the bee sting- induced reversible prothrombotic state was the cause of liver cell injury in our case. However, it is difficult to prove, as Doppler

ultrasound revealed normal hepatic veins and she had never had hypotension or anaphylaxis. Recently, bee sting-induced anaphylaxis, severe hypotension and subsequent sigmoid colon ischemia has been reported by Park *et al*[3]. Given the fact that our patient had never had hypotension during her illness, this mechanism does not seem to be operative in the causation of liver cell injury. Making the issues of bee sting still more complex, there is a report of thrombocytopenic purpura following bee stings, with the platelet count dropping to as low as 15000 and the patient requiring hospitalization and platelet transfusion to stop bleeding[10]. Among the neurological toxicities there are reports of optic neuritis to pontine hemorrhage following the introduction of bee venom[11]. It shows clearly that there is a varied response to bee stings in humans. Bee stings can trigger a prothrombotic or hemorrhagic phenomenon, depending upon the type of species or hither to unknown host factors. There are reports of non traumatic rhabdomyolysis presenting as acute renal failure following bee sitting[12]. Kidney function tests on the index case gave normal results, and her platelet count was also normal. It is pertinent to mention that the patient gradually recovered and the toxicity was reversible. She had high anti nuclear antibody ANA titers on presentation, with a serial drop, and, finally, ANA and other immune marker levels became negative without any specific intervention. This causes us to speculate on the existence of a reversible, transient autoimmune phenomenon having been triggered by the bee sting, causing liver cell damage; however, this theory needs further proof. Whatever the mechanism, the index case experienced a severe liver cell toxicity following bee sting therapy, as her entire etiological profile was non-contributory. Advocates of apitherapy (bee venom as therapy) claim many beneficial effects of bee venom. In a Chinese study[13] of 100 patients with rheumatoid arthritis, where, in addition to the usual medication, bee sting therapy was used, it was found to be beneficial and was shown to reduce analgesic demand and morning stiffness when compared to the group where only medications were used. The authors in this study concluded that bee sting therapy is beneficial in rheumatoid arthritis. There are reports of relief in post- herpetic neuralgia following bee sting therapy. It has been shown that bee sting therapy has anti-nociceptive and anti-inflammatory properties; however, it needs further investigation before it can be used as a modality for postherpetic neuralgia[1].

Bee keepers can form an interesting cohort to study the toxicity of bee sting envenomation. It is felt that persons dealing with bees need to be sensitized so that they do not fall prey to the serious side effects of bee stings, especially anaphylaxis. Münstedt *et al*[14] conducted a study among 73 bee keepers and demonstrated that, after desensitization, there is a complete absence of symptoms following re-exposure to bee stings. Successful immunotherapy to prevent severe anaphylaxis after a bee sting, in combination with omalizumab, an anti-immunoglobulin E monoclonal antibody, has also been reported[15].

In conclusion, it may be said that the present case brings to the fore the various manifestations of bee sting envenomation as well as the need for systematic studies to examine its pathogenesis.

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CASE REPORT

A histologically proven case of progressive liver sarcoidosis with variceal rupture

Hitoshi Yoshiji, Kou Kitagawa, Ryuichi Noguchi, Masahito Uemura, Yasuhide Ikenaka, Yosuke Aihara, Keisuke Nakanishi, Yusaku Shirai, Chie Morioka, Hiroshi Fukui

Hitoshi Yoshiji, Kou Kitagawa, Ryuichi Noguchi, Masahito Uemura, Yasuhide Ikenaka, Yosuke Aihara, Keisuke Nakanishi, Yusaku Shirai, Chie Morioka, Hiroshi Fukui, Third Department of Internal Medicine, Nara Medical University, Kashihara, Nara 634-8522, Japan

Author contributions: Yoshiji H and Kitagawa K described the clinical case, obtained informed consent from the patient, conceived the study, participated in its design, assisted in data collection, coordinated and helped draft the manuscript; Yoshiji H undertook the literature research and contributed to the writing; Uemura M, Ikenaka Y, Noguchi R, Shirai Y, Aihara Y, Nakanishi K, Morioka C and Fukui H were responsible for the diagnosis, patient management and review.

Correspondence to: Hitoshi Yoshiji, MD, PhD, Third Department of Internal Medicine, Nara Medical University, Shijo-cho 840, Kashihara, Nara 634-8522, Japan. yoshijih@naramed-u.ac.jp
Telephone: +81-744-223051 Fax: +81-744-247122

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Abstract

Sarcoidosis is a chronic multi-systemic granulomatous disease, and liver involvement frequently occurs. in most cases, no evidence of liver dysfunction is observed, and portal hypertension due to sarcoid liver diseases is a rareoccurrence. Moreover, no case of liver sarcoidosis has ever been reported with confirmation of the disease progression. Herein we describe a patient having hepatic sarcoidosis with severe portal hypertension and liver dysfunction. The diagnosis was histologically confirmed from granulomatous status to established liver cirrhosis over 10 years. A 46-year-old woman developed massive hematemesis due to the rupture of gastric cardial varices. She underwent emergency endoscopic injection sclerotherapy, and clear evidence of chronic hepatic failure. Twelve years ago, she was diagnosed as having sarcoidosis with respiratory clinicalsymptoms. Liver biopsy revealed asymptomatic incidental granulomas without fibrosis development. After a couple of years, features of liver dysfunction were manifest and progressed. Ten years after the first biopsy, a second liver biopsy was performed, and well established dense fibrosis was revealed. Although significant liver dysfunction with portal hypertension is rarely seen in sarcoidosis, this case indicates that we have to consider the possibility that sarcoidosis may cause end-stage liver cirrhosis.

Key words: Liver sarcoidosis; Portal hypertension; Hepatic failure; Liver cirrhosis

Peer reviewers: Hitoshi Maruyama, MD, Department of Medicine and Clinical Oncology, Chiba University Graduate School of Medicine, 1-8-1, Inohana, Chuou-ku, Chiba, 260-8670, Japan; Hong-Zhi Xu, MD, PhD, Department of Surgery, Massachusetts General Hospital, Shriners Burn Hospital at Boston 51 Blossom Street, Boston, MA 02148, United States

Yoshiji H, Kitagawa K, Noguchi R, Uemura M, Ikenaka Y, Aihara Y, Nakanishi K, Shirai Y, Morioka C, Fukui H. A histologically proven case of progressive liver sarcoidosis with variceal rupture. *World J Hepatol* 2011; 3(10): 271-274 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i10/271.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i10.271

INTRODUCTION

Sarcoidosis is a systemic disease of unknown etiology related to exaggerated cellular immunological reactions, and is characterized by multiple occurrences of non-caseating epithelioid granulomas in several organs, among which the liver is the most frequently affected[1-3]. In the majority of cases, liver dysfunction is usually mild and transient, and the condition is clinically silent. The diag-

nosis of liver sarcoidosis is difficult, because symptoms or functional derangement due to the involvement of the liver are uncommon in sarcoidosis[1-3]. Only a few such patients have exhibited progressive clinical features such as portal hypertension. Liver cirrhosis and variceal bleeding develop in less than 1% of these cases but can be life-threatening complications of hepatic sarcoidosis[4]. To date, the progression of liver sarcoidosis could be followed up in only a few cases. Herein we report a case in which histological examination successfully confirmed the progression of liver sarcoidosis from granulomatous status without fibrosis development, to established liver cirrhosis with dense fibrosis septa over a period of 10 years. The patient had severe clinical manifestations, chronic hepatic failure and variceal rupture.

CASE REPORT

A 46-year-old woman developed massive hematemesis and was admitted to our hospital. Emergency endoscopic examination revealed active bleeding from gastric cardial variceal rupture (Figure 1A). She underwent emergency endoscopic injection sclerotherapy (EIS) (Figure 1B). She had several clinical manifestations of decompensated liver cirrhosis, such as ascites. The laboratory data on admission showed severe liver dysfunction (Table 1). The etiology of the chronic hepatic failure was not clear from the laboratory data since the hepatitis virus markers including hepatitis B and hepatitis C were all negative, and immunological tests, such as anti-nuclear antibody and anti-mitochondrial antibody were negative as well. Twelve years ago, she had been diagnosed as having sarcoidosis with respiratory clinical manifestations. At the time, she was treated with steroid therapy, the respiratory manifestations improved, and finally, after 2 years treatment, the steroid could be tapered off.. At that time, the liver biopsy revealed non-caseating granulomas in the liver without fibrosis development. Aggregates of epithelioid histiocytes and Langhans-type giant cells were observed, surrounded by lymphocytes (Figure 2A). Enhanced computed tomography (CT) showed multiple low-attenuation areas up to 10 mm in diameter, indicating multiple granulomas in the liver. There was no splenomegaly at this time (Figure 2B). Although the steroid therapy achieved some improvement of the respiratory symptoms, liver dysfunction in this patient persisted. Since the liver dysfunction had progressed [alanine aminotransferase/aspartate aminotransferase 68/75 IU/L, alkaline phosphatase (ALP) 813 IU/L, T-Bil 21 mg/L] a second liver biopsy was performed, 10 years after the first biopsy. The second biopsy revealed pseudo-lobular dense fibrosis with persistent moderate infiltration (Figure 3A). The CT findings significantly changed as well. Enhanced CT scanning at the second biopsy showed a marked splenomegaly, and the surface of the liver was irregular, indicating portal hypertension and liver cirrhosis, respectively (Figure 3B). After a couple of sessionsof EIS and interventional therapy, endoscopic findings of the varices alleviated.

Table 1 The Laboratory data on admission

Items tested	Results	
	Patient	Normal
Blood cell count		
WBC (/μL)	3200	3900-9800
RBC (× 10^4/μL)	256	427-570
Hb (g/dL)	9.0	13.5-17.6
Plt (× 10^4/μL)	8.6	13.1-36.2
Coagulation function		
PT (s)	18.7	10-15
Viral examination		
HBsAg	(-)	(-)
HBV-DNA	(-)	(-)
HCV Ab	(-)	(-)
Biochemical parameters		
CRP (mg/dL)	0.6	< 0.2
TP (g/dL)	7.2	6.4-8.1
Alb (g/dL)	3.1	4.0-5.1
ZTT (KU)	21.5	3-13
AMY (IU/L)	72	40-200
AST (IU/L)	70	12-32
ALT (IU/L)	36	5-36
LDH (IU/L)	225	116-250
ALP (IU/L)	924	115-359
γ-GTP (IU/L)	145	11-69
ChE (IU/L)	98	192-446
TG (mg/dL)	36	30-150
T-Ch (mg/dL)	125	120-240
BUN (mg/dL)	34	8-20
CRE (mg/dL)	0.75	0.53-1.01
Na (mEq/L)	137	137-146
K (mEq/L)	4.8	3.6-4.8
T-Bil (mg/dL)	4.8	0.3-1.1
NH3 (μg/dL)	145.7	12-66
ACE (U/L)	17.5	8.3-21.4
FBS (mg/dL)	85	60-100
HbA1c (%)	4.10	4.3-5.8
Fe (μg/L)	37.7	3.6-114

WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Plt: Platelet; PT: Prothrombin time; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CRP: C-reactive protein; TP: Total protein; Alb: Albumin; ZTT: Zinc sulfate turbidity test; AMY: Amylase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; γ-GTP: γ-glutamyltransfesrase; ChE: Cholinesterase; TG: Triglyceride; T-Ch: Total cholesterol; BUN: Blood urine nitrogen; CRE: Creatinine; ACE: Angiotensin-converting enzyme; FBS: Fasting blood sugar.

DISCUSSION

In this case, we observed that the liver sarcoidosis progressed from the granulomatous status without fibrosis to established liver cirrhosis associated with severe portal hypertension and hepatic failure. Portal hypertension is an uncommon finding in sarcoidosis, and the mechanisms involved are not completely understood. Several reports have suggested that hepatic granulomas may play an important role under certain conditions[5]. Granulomas are the main histological features of sarcoidosis. The granulomatous lesions in hepatic sarcoidosis are usually very small and asymptomatic. However, in a few cases, chronic intrahepatic cholestasis may develop. Intrahepatic cholestasis has been reportedly detected in up to half of

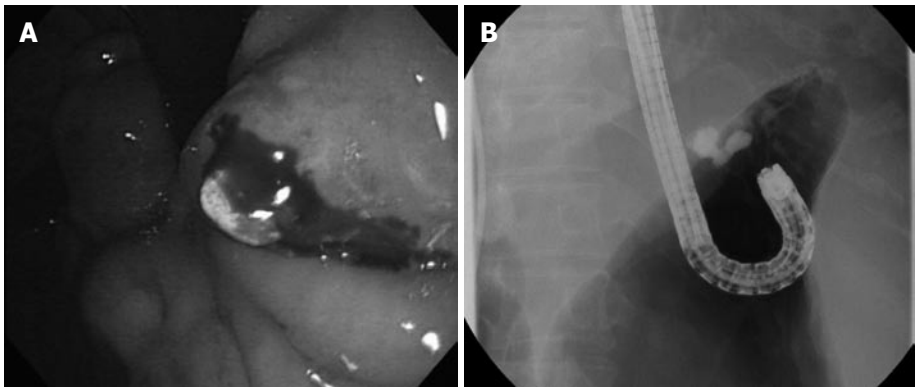

Figure 1 Endoscopic examination at the time of cardial cariceal rupture. A: Endoscopic examination revealed active bleeding consequent to gastric cardial variceal rupture; B: Radiographic image of emergency endoscopic injection sclerotherapy with 5% ethanolamine oleate with iopamidol.

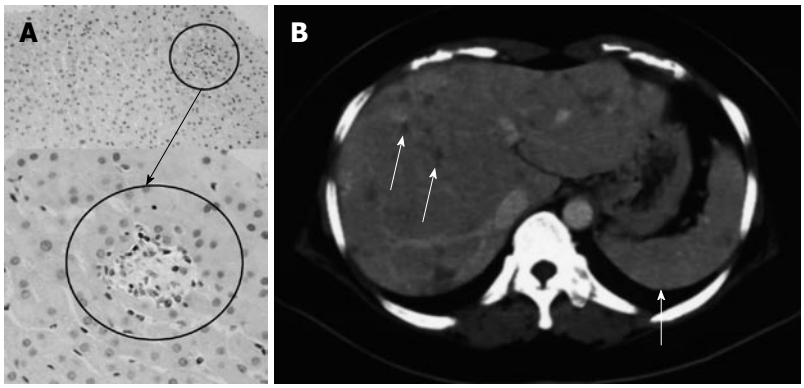

Figure 2 First histological examination of the liver, and the image of enhanced computed tomogram. A: The first liver biopsy showed non-caseating granulomas in the liver without fibrosis development. Aggregates of epithelioid histiocytes and Langhans-type giant cells were observed surrounded by lymphocytes. The original magnifications are × 40 and × 200, respectively; B: Enhanced computed tomogram showing multiple low-attenuation areas up to 10 mm in diameter, indicating multiple granulomas in the liver (white arrows). There was no splenomegaly at this time.

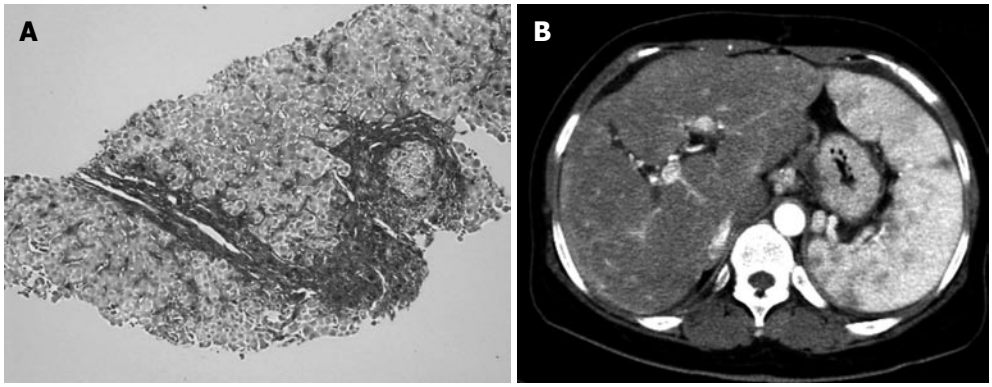

Figure 3 Second histological examination of the liver, and the image enhanced computed tomogram. A: The second biopsy revealed pseudo-lobular dense fibrosis with moderate infiltrating cells; B: The images of the enhanced computed tomography (CT) were significantly altered, too. The enhanced CT at the second biopsy showed a marked splenomegaly, and the surface of the liver was irregular, indicating portal hypertension and liver cirrhosis, respectively.

the biopsy specimens. Cholestasis may result from hepatic granulomas, or involvement of the intra- or extrahepatic biliary tract by sarcoid, or compression of the common bile duct by enlarged peri-hilar lymph nodes. Chronic cholestasis and the possible coexistence of other liver-damaging diseases have been suggested as causes of the liver cirrhosis and portal hypertension. However, this was not the case in our patient, since the liver biopsy revealed no intrahepatic cholestasis (ALP 148 IU/L, γ-guanosine triphosphate 68 IU/L, T-Bil 11 mg/dL). Furthermore, the granulomatous cholangitis which represent vanishing bile ducts was not observed either.

Alternatively, portal hypertension in liver sarcoidosis may be attributed to obstruction of the portal flow, be-

cause of granulomas in the portal area causing a presinusoidal block. A granulomatous phlebitis obstructing the portal and hepatic veins may lead to ischemia and parenchymal extinction[6,7]. Portal vein thrombosis sometimes happens in liver sarcoidosis perhaps because of stasis consequent to the obliteration of small portal veins. Budd-Chiari syndrome may also develop because of extrinsic compression of the hepatic veins by sarcoid granulomas, causing narrowing of the veins, venous stasis, and subsequent thrombosis[6,7]. In these cases, most of the patients develop portal hypertension not associated with liver cirrhosis. The second biopsy in our patient demonstrated a pseudo-lobular fibrotic septa and cirrhosis, and the laboratory data were in compliance with the histological findings, indicating that deregulation of these vessels was not the trigger of portal hypertension in our patient. In the CT image, no severe stricture such as hepatic vein and/or inferior vena cava (data not shown) could be observed. However, there is a limitation in this patient, since we did not measure the HVPG by hepatic venography.

In general, corticosteroids are employed for treatment of sarcoidosis when organ function is threatened, although the role of corticosteroids in the treatment of hepatic sarcoidosis is unclear[6,8]. Although these drugs improve lung function, their effects on hepatic sarcoidosis are difficult to assess. Our patient was first diagnosed as having lung sarcoidosis and received corticosteroid therapy[9]. The respiratory clinical manifestations were improved by administration of corticosteroids, but then the liver dysfunction started. It has been reported that corticosteroids may improve the results of liver function tests in those with mild to moderate abnormalities[10], but without any consistent clinical or pathologic effects in those with severe disturbances[11]. In spite of the biochemical improvement, the liver biopsy may show progression of the disease[1]. In our patient, her second biopsy showed significant progression even though the respiratory clinical manifestations improved. Treatment of hepatic sarcoidosis with corticosteroids tends to reduce the liver size and the number of hepatic granulomas[12], but does not alleviate portal hypertension[11,13,14]. Although the exact mechanisms were not clear at this time, corticosteroid treatment may have been involved in the progression of hepatic sarcoidosis in this case. Accumulation of cases of hepatic sarcoidosis with disease progression would be required to elucidate the mechanistic insights in the future.

In conclusion, we herein report the first case of hepatic sarcoidosis with severe portal hypertension and liver dysfunction. The diagnosis was histologically confirmed from the granulomatous status, progressing to established liver cirrhosis over 10 years. Although significant liver dysfunction with portal hypertension is rarely seen in sarcoidosis, we have to consider the possibility that sarcoidosis may cause end-stage liver cirrhosis.

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Revisiting acute liver injury associated with herbalife products

Kristy Appelhans, Casey Smith, Ezra Bejar, Y Steve Henig

Kristy Appelhans, Department of Product Compliance and Safety, Herbalife International of America Inc., Torrance, CA 90502, United States
Casey Smith, Ezra Bejar, Scientific Affairs, Herbalife International, Torrance, CA 90502, United States
Y Steve Henig, Chief Scientific Officer, Herbalife International, Torrance, CA 90502, United States
Author contributions: Appelhans K wrote the paper; Smith C, Bejar E and Henig YS contributed equally as editors and reviewers of the paper.
Correspondence to: Kristy Appelhans, NMD, Department of Product Compliance and Safety, Herbalife International of America Inc., 990 West 190th Street Suite 650, Torrance, CA 90502, United States. kristyr@herbalife.com
Telephone: +1-310-7192458 Fax: +1-310-7673375
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Abstract

In the November 27, 2010 issue of the *World Journal of Hepatology (WJH)*, three case reports were published which involved patients who had consumed various dietary supplements and conventional foods generally marketed as weight loss products. The reference to Herbalife products as contaminated and generally comparable to all dietary supplements or weight loss products is not scientifically supported. The authors provided an insufficient amount of information regarding patient histories, concomitant medications and other compounds, dechallenge results, and product specifications and usage. This information is necessary to fully assess the association of Herbalife products in the *WJH* case reports. Therefore, the article does not objectively support a causal relationship between the reported cases of liver injury and Herbalife products or ingredients.

Key words: Herbalife; Liver; Hepatotoxicity; Weight loss products; Dietary supplements

Peer reviewer: Jordi Muntané, PhD, Unidad de Investigacion, Hospital Universitario Reina Sofía, Av. Menéndez Pidal s/n, Cordoba 14004, Spain

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TO THE EDITOR

In the November 27, 2010 issue of the *World Journal of Hepatology* (*WJH*), three case reports were published which involved patients who had consumed various dietary supplements and conventional foods generally marketed as weight loss products. Case 1 involved a patient who did not consume Herbalife products, while Cases 2 and 3 each reportedly consumed various Herbalife products. Herbalife fundamentally disagrees with the conclusions made by the authors with regard to any cause and effect relationship related to the intake of Herbalife products. First, Herbalife is not a single product and no unique suspect product or ingredient has been implicated in this paper amongst the reported cases. In addition, the authors arbitrarily compared cases involving the use of a single product (Hydroxycut) with patients who consumed a group of totally unrelated products produced by the company Herbalife. To bundle a brand of products such as Herbalife with another company that sells different products simply because they are all dietary supplements is not valid. Finally, there are specific considerations, in regard to the two patients who consumed Herbalife products, that would render many of the observations and conclusions discussed by the authors as speculative and unsubstantiated. The specific and factual points supporting these views are further detailed below.

Case 2 describes a 37-year-old female who developed symptoms of abdominal pain, mild nausea, and painless

jaundice 1 mo prior to presenting at the hospital[1]. Several pertinent negatives were disclosed by the authors, including autoimmune markers and viral serology. According to the authors, the patient did not report any pre-existing medical conditions for which the onset had preceded the use of Herbalife products. However, the pathology assessment concluded that this patient's biopsy result was consistent with chronic liver disease, in which case Herbalife products were thought to have had an additive effect. This opinion contradicts repeated statements by the authors that acute liver injury in each case report was due to the use of herbal weight loss products. In addition, the etiology of the pre-existing condition was not identified by the authors, and there was no discussion regarding the role of the condition in the acute onset of her symptoms. Furthermore, the dosage and frequency at which this patient consumed Herbalife products is unknown. Finally, the inconsistency of the objective findings with the patient's reported medical history would suggest that further investigation is warranted. This should include a review of the patient's pre-existing condition, potential use of medications prescribed for her condition, other compounds she may have been consuming, and the status of her health prior to the reported incident. In the absence of the aforementioned data, the exclusion of possible differential diagnoses is not well-supported.

Case 3 describes a 53-year-old female who developed symptoms of painless jaundice and pruritus 3 wk prior to presenting at the hospital[1]. This patient denied family history of liver disease, but no discussion was provided regarding her own medical history, other than the fact that she reportedly denied the use of alcohol and did not engage in "illicit substance abuse". The authors further stated that the patient had not been prescribed any new medications, which implies that she may have been taking other agents concomitantly. However, information regarding the use of concomitant medications, or the conditions for which she may have been receiving treatment, was not disclosed. Such information is critical and should have been obtained through follow-up review of the patient's previous medical records. Without this information, it is unknown whether concomitant medication(s) were withdrawn and/or accounted for during the dechallenge process. The patient's use of Herbalife products was also not specified by product names and it is unknown whether the dosage and frequency of consumption was adherent to recommendations indicated on the product label(s). In addition to the absence of the aforementioned pertinent patient data, there are various refutable facts that remain in regard to the comments and conclusions made by the authors.

In their *WJH* article, the authors concluded that it was difficult to isolate a single ingredient or mechanism associated with acute liver injury for either patient consuming Herbalife products[1]. In an effort to discuss potential causative agents for the reported conditions in these patients, the authors extraneously reference previously published case reports involving Herbalife products, including those of two consumers who reportedly developed hepatotoxicity following exposure to *Bacillus subtilis* (*B. subtilis*)[2].

In review of this reference, it has been noted that there were various critical deficiencies in the scientific methodology used to isolate *B. subtilis* in the Herbalife samples reported to have been contaminated. For example, a dose dependent increase in LDH leakage in HepG2 cells was observed in the experimental assay, but investigators did not present any control data for their experiments, nor did they present any data that suggested this assay is a valid proxy for liver injury in healthy individuals "*in vivo*". Neither patient reported symptoms consistent with classical *B. subtilis* food poisoning and they did not report testing the product for the detection of cerulide or any of the reported heat-stable toxins associated with certain strains of *B. subtilis*. Furthermore, the investigators did not enumerate the levels of *B. subtilis* in the products tested or report testing relevant specimens from the patients for these organisms or their toxins. This was a crucial step missing in the reported investigation as all previous documented reports find that high levels of the organism must be consumed to cause illness. Herbalife products, consumed by the patients described in the *WJH* article, to date show no evidence of *B. subtilis* contamination. *B. subtilis* infections are relatively rare and seldom contracted through food sources. This bacterium is actually ubiquitous in nature and generally recognized as safe with a history of safe use in food, and is considered to be safe for the production of enzymes or ingredients for use in food[3]. There have been reported cases of *B. subtilis*-related gastroenteritis and other complications, usually involving immuno-compromised patients or those with other underlying chronic illnesses, which did not appear to be the case for any of the patients presented in the *WJH* article. Therefore, it is highly unlikely that *B. subtilis* could be the cause or have contributed to the severe hepatotoxicity of patients in either the referenced article or the two patients discussed in the *WJH* article.

The *WJH* authors also suggest intentional or incidental contamination of Herbalife ingredients and identify various potential sources, including unrefined raw herbal extracts, heavy metals, pesticides, and additives[1]. However, some of the additives mentioned as potential contaminants by the authors (e.g., flavoring, colors, and preservatives) are commonly used and well-documented industry-wide as safe for consumption in conventional foods, as well as dietary supplements,. In addition, authors also reference an article from 2002 that reviews possible contamination sources inherent to herbal remedies marketed without proper quality control measures in place[5]. Herbalife is not specifically implicated in the referenced article, yet the authors imply that Herbalife product contamination and lack of quality control contributed to the liver injury. The authors' assumption is wrong and does not take into consideration that the United States FDA requires dietary supplement manufacturers to use current Good Manufacturing Practices (cGMPs) in the produc-

tion of dietary supplements[4]. The goal of these regulations is to "ensure that a dietary supplement contains what the manufacturer intends" and meets specifications to ensure the dietary supplement contains the correct ingredient, purity, strength and composition intended. Herbalife has rigorous processes in place concerning quality control, including extensive safety reviews based on existing literature for product ingredients, testing to confirm that labeled ingredients are present in finished goods, and to assure all tested ingredients meet product specifications on an ongoing basis. In addition to complying with cGMP regulations, Herbalife acts in accordance with other generally recognized industry standards or requirements by sourcing and testing raw materials to further ensure that the final product complies with specifications for identity, purity, potency and contaminants.

The authors also try to implicate the *Camellia sinensis* (*C. sinensis*) used in Herbalife's tea drink products by citing case reports of liver injury in association with ethanolic extracts of *C. sinensis*, which contain a concentrated fraction of EGCG[1]. The most important safety consideration for green tea is the extraction method. The historical data supporting the safety of green tea is based on the consumption of an aqueous extract over thousands of years, specifically, the typical three cups per day that are commonly consumed in Asian countries. Aqueous extracts of green tea are quite different from solvent extractions, which are commonly used to concentrate select fractions of green tea, such as EGCG or caffeine. Again, the *WJH* authors have not considered the clinical significance of potential differences in raw material processing amongst manufacturers, controls for contamination and identification of raw materials, and the implication of these differences when reviewing published case reports of liver injury. In addition, the authors state that Herbalife has refused to provide detailed analyses of ingredients and formulations, although no attempt was made by these authors to contact Herbalife to obtain further information regarding Herbalife products or ingredients. Herbalife has, to date, remained compliant with all formal regulatory requests and requirements for product information.

The authors state that significant liver injury induced by herbal supplements is a rare event[1]. This statement is true as approximately 20 to 50 percent of all cases presenting as hepatotoxicity are cryptogenic leading to the incidental association of liver disease with a group of products in the absence of specific evidence[5]. While this disease is the most common cause of drug withdrawal during post-marketing surveillance, it is an uncommon cause of liver disease. The background incidence of hepatotoxicity in populations is clearly comparable to the reported incidence of immunoallergic and individualistic reactions to allergens in foods, supplements, or the environment. For example, in a study of 71 000 North Americans in 1992, the background rate of idiopathic or cryptogenic liver disease was 24 cases per 100 000 individuals compared to 14 per 100 000 attributed to cases of hepatitis B, 25 per 100 000 due to alcoholism, and 7 per 100 000 to other viral illnesses[6]. While the spectrum of liver diseases may well have changed since 1992 when this survey was done, idiopathic liver disease remains a significant percentage of all cases. Therefore, it is particularly important in making such associations to have incontrovertible evidence such as is often available for prescription drugs where, under controlled conditions, a cause-effect relationship can be established.

Finally, the authors also state that existing case reports of dietary supplement-induced hepatotoxicity include patients with pre-existing liver disease and that weight loss supplements could worsen such conditions in these patients. However, this effect could occur from many different substances, including over-the-counter and prescription medications, as these patients may be "pre-sensitized" due to an underlying hepatic condition.

In conclusion, the reference to Herbalife products as contaminated and generally comparable to all dietary supplements or weight loss products is not scientifically supported. Further information regarding patient histories, concomitant medications and other compounds, dechallenge results, and product specifications and usage is indicated to assess fully the association of Herbalife products in the *WJH* case reports. Therefore, the article does not objectively support a causal relationship between the reported cases of liver injury and Herbalife products or ingredients.

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Canhua Huang, PhD, Oncoproteomics Group, The State Key Laboratory of Biotherapy, Sichuan University, No. 1 Keyuan Rd 4, Gaopeng ST, High Tech Zone, Chengdu 610041, Sichuan Province, China

Iryna S Hepburn, MD, Gastroenterology and Hepatology, Medical College of Georgia, Augusta, GA1205 Sumter Landing Lane, Evans, GA 30809, United States

Pietro Invernizzi, MD, PhD, Division of Internal Medicine and Hepatobiliary Immunopathology Unit, IRCCS Istituto Clinico Humanitas, via A. Manzoni 113, 20089 Rozzano, Milan, Italy

Rachel Mary Hudacko, MD, Department of Pathology and Laboratory Medicine, Medical Education Building, Room 212, Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place, New Brunswick, NJ 08901, United States

Regina Coeli dos Santos Godenberg, PhD, Associate Professor of Physiology, Carlos Chagas Filho Biophysics Institute, Federal University of Rio de Janeiro, Av. Carlos Chagas Filho no 373, CCS, Bloco G, sala G2-053, 21941902 Rio de Janeiro, Brazil

Sandro Vento, MD, Professor of Internal Medicine, Department of Internal Medicine, School of Medicine, Faculty of Health Sciences, University of Botswana, Private Bag 0022, Gaborone, Botswana

Stacee Marie Lerret, PhD, RN, CPNP, Liver Transplant Coordinator, Division of Gastroenterology, Hepatology and Nutrition Children's Hospital of Wisconsin, Medical College of Wisconsin, 8701 West Watertown Plank Road, Milwaukee, WI 53226, United States

Wing-Kin Syn, MD, Hepatologist, 1GI Division, Duke University, Suite 1073, 595 LaSalle Street, Durham 27710, North Carolina, United States

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Miami, FL 33101, United States

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Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11
Regensburg 93053, Germany

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 22, 2011-March 04, 2011
Canadian Digestive Diseases Week 2011
Vancouver, BC, Canada

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

March 3-5, 2011
42nd Annual Topics in Internal Medicine
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Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
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Mayo Clinic Gastroenterology & Hepatology 2011
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March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
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March 25-27, 2011
MedicReS IC 2011
Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease
San Diego, CA 94143, United States

April 25-27, 2011
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Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
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1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671
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22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
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May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn, Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV
SPIGC, II ESYS
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June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
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October 28-November 2, 2011
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INSTRUCTIONS TO AUTHORS

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The major task of *WJH* is to rapidly report the most recent results in basic and clinical research on hepatology, specifically including autoimmune, cholestatic and biliary disease, cirrhosis and its complications, liver biology/pathobiology, liver failure, growth , liver failure/cirrhosis/portal hypertension, liver fibrosis, hepatitis B and C virus infection, hepatocellular carcinoma, biliary tract disease, transplantation, genetics, epidemiology, microbiology and inflammatory disorders, molecular and cell biology, nutrition, geriatric hepatology, pediatric hepatology, steatohepatitis and metabolic liver disease, diagnosis and screening, endoscopy, imaging and advanced technology.

Columns

The columns in the issues of *WJH* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in hepatology; (9) Brief Article: To briefly report the novel and innovative findings in hepatology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJH*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of hepatology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in hepatology.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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