

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 July 14; 23(26): 4661-4846



### EDITORIAL

- 4661** Can a fibrotic liver afford epithelial-mesenchymal transition?

*Munker S, Wu YL, Ding HG, Liebe R, Weng HL*

- 4669** Impact of hepatitis C oral therapy in portal hypertension

*Libânio D, Marinho RT*

### REVIEW

- 4675** Present and future of metastatic colorectal cancer treatment: A review of new candidate targets

*Martini G, Troiani T, Cardone C, Vitiello P, Sforza V, Ciardiello D, Napolitano S, Della Corte CM, Morgillo F, Raucci A, Cuomo A, Selvaggi F, Ciardiello F, Martinelli E*

- 4689** Diarrhea after bariatric procedures: Diagnosis and therapy

*Borbély YM, Osterwalder A, Kröll D, Nett PC, Inglin RA*

### ORIGINAL ARTICLE

#### Basic Study

- 4701** Fibrinogen deficiency suppresses the development of early and delayed radiation enteropathy

*Wang J, Pathak R, Garg S, Hauer-Jensen M*

- 4712** *Helicobacter pylori* vacA genotype is a predominant determinant of immune response to *Helicobacter pylori* CagA

*Link A, Langner C, Schirrmeister W, Habendorf W, Weigt J, Venerito M, Tammer I, Schlüter D, Schlaermann P, Meyer TF, Wex T, Malfertheiner P*

- 4724** Jianpi Qingchang decoction regulates intestinal motility of dextran sulfate sodium-induced colitis through reducing autophagy of interstitial cells of Cajal

*Dai YC, Zheng L, Zhang YL, Chen X, Chen DL, Wang LJ, Tang ZP*

- 4735** *Lactobacillus acidophilus* alleviates pouchitis after ileal pouch-anal anastomosis in rats

*Xu YY, Zhang YY, He AQ, Li KY, Gao SY, Liu G*

- 4744** Effect of EPEC endotoxin and bifidobacteria on intestinal barrier function through modulation of toll-like receptor 2 and toll-like receptor 4 expression in intestinal epithelial cell-18

*Yang X, Gao XC, Liu J, Ren HY*

### Retrospective Cohort Study

- 4752 Hospital costs, length of stay and prevalence of hip and knee arthroplasty in patients with inflammatory bowel disease  
*Ehrenpreis ED, Zhou Y*

### Retrospective Study

- 4759 Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naïve hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million IU/mL: Single center, real world effectiveness and safety  
*Latt NL, Yanny BT, Gharibian D, Gevorkyan R, Sahota AK*
- 4767 Early radiological assessment of locally advanced pancreatic cancer treated with electrochemotherapy  
*Granata V, Fusco R, Setola SV, Piccirillo M, Leongito M, Palaia R, Granata F, Lastoria S, Izzo F, Petrillo A*
- 4779 Effect of initial stent position on patency of transjugular intrahepatic portosystemic shunt  
*Luo SH, Chu JG, Huang H, Yao KC*

### Observational Study

- 4788 Endoscopy is of low yield in the identification of gastrointestinal neoplasia in patients with dermatomyositis: A cross-sectional study  
*Kidambi TD, Schmajuk G, Gross AJ, Ostroff JW, Terdiman JP, Lee JK*
- 4796 Levels and activities of von Willebrand factor and metalloproteinase with thrombospondin type-1 motif, number 13 in inflammatory bowel diseases  
*Cibor D, Owczarek D, Butenas S, Salapa K, Mach T, Undas A*
- 4806 Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients  
*Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G*
- 4815 Extreme liver resections with preservation of segment 4 only  
*Balzan SMP, Gava VG, Magalhães MA, Dotto ML*
- 4823 Predictive factors for body weight loss and its impact on quality of life following gastrectomy  
*Tanabe K, Takahashi M, Urushihara T, Nakamura Y, Yamada M, Lee SW, Tanaka S, Miki A, Ikeda M, Nakada K*

### Prospective Study

- 4831 Divergent expression of bacterial wall sensing toll-like receptors 2 and 4 in colorectal cancer  
*Paarnio K, Väyrynen S, Klintrup K, Ohtonen P, Mäkinen MJ, Mäkelä J, Karttunen TJ*
- 4839 Non-invasive assessment of liver fibrosis using two-dimensional shear wave elastography in patients with autoimmune liver diseases  
*Zeng J, Huang ZP, Zheng J, Wu T, Zheng RQ*

## Contents

*World Journal of Gastroenterology*  
Volume 23 Number 26 July 14, 2017

### ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Seung-Wan Ryu, MD, PhD, Associate Professor, Division of Gastrointestinal Surgery, Department of Surgery, Keimyung university, Sch Med, Daegu 700-712, South Korea

### AIMS AND SCOPE

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

### INDEXING/ABSTRACTING

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

### FLYLEAF

#### I-IX Editorial Board

### EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*  
Responsible Electronic Editor: *Dan Li*  
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Yuan Qi*  
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL  
*World Journal of Gastroenterology*

ISSN  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

LAUNCH DATE  
October 1, 1995

FREQUENCY  
Weekly

EDITORS-IN-CHIEF  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

EDITORIAL BOARD MEMBERS  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE  
Jin-Lei Wang, Director  
Yuan Qi, Vice Director  
Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

PUBLISHER  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE  
July 14, 2017

COPYRIGHT  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION  
<http://www.f6publishing.com>

## Retrospective Study

**Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naïve hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million: Single center, real world effectiveness and safety**

Nyan L Latt, Beshoy T Yanny, Derenik Gharibian, Rita Gevorkyan, Amandeep K Sahota

Nyan L Latt, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, Jacksonville, FL 32224, United States

Beshoy T Yanny, Amandeep K Sahota, Division of Gastroenterology and Hepatology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA 90027, United States

Derenik Gharibian, Pharmacy Operations Office, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA 90027, United States

Rita Gevorkyan, Department of Clinical Operations, Kaiser Permanente Southern California, CA 91107, United States

**Author contributions:** Latt NL and Sahota AK designed the research; Latt NL and Yanny BT performed the data abstraction, contributed to the analysis; Latt NL wrote the paper; Gharibian D and Sahota AK provided clinical advice and supervised the report; Gevorkyan R helped with the data abstraction and provided clinical advice.

**Institutional review board statement:** This study was reviewed and approved by Kaiser Permanente Southern California Institutional Review Board.

**Informed consent statement:** Patients were not required to give informed consent to the study. The study was qualified for an 'exempt status' by the Institutional Review Board due to its retrospective nature. We collected only the existing data from electronic medical records, the data were stored without any patient identifiers.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** 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/>

**Manuscript source:** Invited manuscript

**Correspondence to:** Nyan L Latt, MD, Transplant Hepatology Fellow, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States. [latt.nyan@mayo.edu](mailto:latt.nyan@mayo.edu)  
**Telephone:** +1-904-9563256  
**Fax:** +1-904-9563359

**Received:** January 16, 2017  
**Peer-review started:** January 18, 2017  
**First decision:** February 9, 2017  
**Revised:** March 8, 2017  
**Accepted:** June 9, 2017  
**Article in press:** June 12, 2017  
**Published online:** July 14, 2017

**Abstract****AIM**

To evaluate sustained viral response (SVR) of 8-wk ledipasvir/sofosbuvir therapy among non-cirrhotic, genotype-1 hepatitis C virus (HCV) patients with RNA < 6 million IU/mL.

**METHODS**

We performed a retrospective cohort study to examine SVR rates, predictors of treatment failure and safety analysis of 8-wk ledipasvir/sofosbuvir (LDV/SOF) therapy



among non-cirrhotic, genotype 1 HCV patients with viral load < 6 million IU/mL. Primary outcome was an achievement of SVR at 12 wk after treatment. Secondary outcomes were identifying predictors of treatment failure and adverse events during treatment.

## RESULTS

Total 736 patients: 55% males, 51% Caucasians and 65% were genotype 1a. Non-cirrhotic state of 53% was determined by clinical judgment (imaging, AST, platelet count) and 47% had documented liver fibrosis testing (biopsy, vibration-controlled transient elastography, serum biomarkers). Overall SVR12 was 96%. No difference in SVR12 was seen between patients whose non-cirrhotic state was determined by clinical judgment and patients who had fibrosis testing. Age groups, gender, ethnicity and genotype 1 subtype did not predict SVR. Non-cirrhotic state determined by clinical judgment based on simple, non-invasive tests were not associated with lower SVR [OR = 1.02, 95%CI: 0.48-2.17,  $P = 0.962$ ]. The AUROC for hepatitis C RNA viral load was 0.734 ( $P < 0.001$ , 95%CI: 0.66-0.82). HCV RNA 2.2 million IU/mL was identified as the cutoff value with sensitivity 73% and specificity 64%. HCV RNA < 2.2 million IU/mL was associated with significantly higher SVR 98% with OR = 0.22 (95%CI: 0.1-0.49,  $P < 0.001$ ) compared to SVR 92% in HCV RNA  $\geq$  2.2 million IU/mL. No death or morbidities were reported.

## CONCLUSION

Our outcomes validate safety and effectiveness of 8-wk LDV/SOF therapy in non-cirrhotic, untreated HCV genotype 1 patients with HCV RNA < 6 million IU/mL.

**Key words:** Hepatitis C; Sustained viral response; Ledipasvir; Cirrhosis; Sofosbuvir

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** We highlight that sustained viral response (SVR) outcomes in patients with their non-cirrhotic status determined by clinical judgment using simple, cheap, non-invasive tests such as platelet count, sonographic finding of spleen size and hepatic morphology, are comparable with those who had specialized tests such as liver biopsy, vibration-controlled transient elastography or specialized serum biomarker test. We also validate the fact that hepatitis C virus (HCV) RNA plays a role in predicting SVR (AUROC = 0.743, 95%CI: 0.66-0.82) with a cutoff value of 2.2 million IU/mL. Significantly higher 98% SVR was observed among HCV RNA < 2.2 million IU/mL, compared to 92% SVR with HCV RNA  $\geq$  2.2 million IU/mL.

Latt NL, Yanny BT, Gharibian D, Gevorkyan R, Sahota AK. Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naïve hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million IU/mL: Single center, real world effectiveness and safety.

*World J Gastroenterol* 2017; 23(26): 4759-4766 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i26/4759.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i26.4759>

## INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of cirrhosis, hepatocellular carcinoma and liver-related mortality<sup>[1]</sup>. Recent studies estimate the prevalence of HCV to be between 1.2%-1.5% in the United States, which is approximately 4.5-5 million. This population is composed of 1 million incarcerated/homeless individuals, hospitalized patients, and people living on Indian reservations, and also includes 3.6 million from the 2003-2010 National Health and Nutrition Examination Survey<sup>[2,3]</sup>. The prevalence of HCV is declining, but HCV-related cirrhosis is still expected to peak in the year 2020<sup>[4]</sup>. Therefore, effective, safe and well-tolerated treatment regimens with shorter duration are urgently needed.

Hepatitis C treatment has evolved from a 78-wk interferon monotherapy to 48-wk pegylated interferon plus ribavirin therapy and now 12-wk therapy with newer all-oral direct-acting antiviral (DAA) agents. DAA regimens have revolutionized the treatment of hepatitis C with their excellent sustained virologic response (SVR), tolerable side effect profiles and shorter duration of therapy. Despite the high cost of newer DAAs, a cost-effective analysis has demonstrated that ledipasvir/sofosbuvir (LDV/SOF)-based regimens will reduce long-term HCV-related complications and are cost-effective in the majority of chronic HCV patients<sup>[5]</sup>.

ION-3 trial demonstrated that an 8-wk LDV/SOF therapy in non-cirrhotic, treatment naïve genotype 1 HCV patients with HCV RNA < 6 million IU/mL is non-inferior to 12-wk LDV/SOF therapy (SVR: 94% vs 95%)<sup>[6]</sup>. The shorter duration of treatment can remarkably increase patient compliance and substantially reduce treatment cost. Real-world studies have reported that SVR rates are comparable to those observed in ION-3 trial<sup>[7-10]</sup>. However, conflicting data has been reported by a large real-world cohort from Veteran's Affairs in which researchers found that non-cirrhotic patients with HCV-RNA < 6 million IU/mL were less likely to achieve SVR with 8-wk LDV/SOF treatment compared to 12-wk treatment<sup>[9]</sup>.

Eight-week LDV/SOF therapy for non-cirrhotic, genotype 1 HCV patients is not included in HCV guidelines by American Association for the Study of Liver Diseases and Infectious Diseases Society of America due to lack of real-world validation for comparable SVR with 12-wk therapy<sup>[11]</sup>. European Association for the Study of the Liver and United States Food and Drug Administration recommend considering 8-wk therapy with caution in treatment-naïve genotype-1 HCV patients without cirrhosis who have pre-treatment viral load < 6 million IU/mL<sup>[12,13]</sup>. We contemplated that

shorter duration of treatment could provide the lower cost, the higher patient compliance and adherence as long as the shorter duration therapy can provide the comparable outcomes. We performed a retrospective cohort study to examine the SVR rates, the predictors of treatment failure and the safety analysis of 8-wk LDV/SOF therapy among non-cirrhotic, previously untreated genotype-1 HCV patients with viral load < 6 million IU/mL.

## MATERIALS AND METHODS

### Study population

Kaiser Permanente Southern California (KPSC) is a large, integrated healthcare system with over 4 million members. Integrated healthcare is delivered to members at 14 medical centers throughout the region. All interactions with the healthcare system, such as clinic/emergency department/urgent care visits, hospital admissions and outpatient laboratory tests are captured in an integrated electronic medical record (EMR) system and the data is available for research purposes. Emergency care delivered at outside facilities is captured in a claims system that is also available. The KPSC Regional guidelines for 8-wk LDV/SOF therapy were developed and all providers were notified for eligibility criteria: genotype-1, non-cirrhotic, HCV-RNA < 6 million IU/mL and no prior treatment failure. Cirrhotic status of some patients was confirmed by liver biopsy or other non-invasive testing such as vibration-controlled transient elastography (VCTE) or FIBROSPECT II test in some KPSC centers. In some patients, non-cirrhotic status of some patients was determined by clinical judgement of treating healthcare providers using sonographic morphology of the liver, the spleen size and the platelet count in other KPSC centers. All patients with platelet count less than  $150 \times 10^9/L$  underwent a form of hepatic fibrosis testing such as liver biopsy, VCTE or FIBROSPECT II. Every patient had hepatic sonography and baseline laboratory testing prior to hepatitis C treatment. We developed a protocol for KPSC nurse practitioners, physician assistants and pharmacists, who specialized in hepatitis C treatment, to document intended treatment duration and rationales, pre-treatment testing and close monitoring of patients during treatment such as laboratory testing every 2 wk, calling/messaging to identify any barriers/adverse events and providing coping mechanisms/strategies if any event occurred.

Inclusion criteria: patients with age  $\geq 18$  years, HCV viral load < 6 million IU/mL, no cirrhosis or prior treatment failure and who had received 8-wk LDV/SOF therapy for chronic HCV genotype-1 infection. Exclusion criteria: patients without SVR12 (SVR at 12 wk after end of treatment) data, patients who did not complete the intended therapy and patients who missed doses for more than seven consecutive days. Individuals who fulfilled above criteria were included in

the final study analysis.

### Study design

We conducted a retrospective cohort study from December 2015 to December 2016, of all patients who had completed 8-wk LDV/SOF therapy. Patient's clinical and demographic information was captured from KPSC-EMR system. We developed a standardized protocol with explicit criteria for data abstraction including pre- and post-treatment laboratory results, co-morbid medical conditions, liver biopsy (Metavir fibrosis staging), VCTE (kilopascal), FIBROSPECT II test (serum biomarkers), adverse events, clinic/urgent care/emergency department visits and hospitalizations during treatment. Two data abstractors, who are familiar with the EMR system, collected the data according to the protocol criteria to maximize the inter-rater reliability of data abstraction.

### Safety analysis

Patient reported side effects such as fatigue, headache, insomnia, arthralgia/myalgia, nausea, cough, rash, dizziness, diarrhea, pruritus, irritability and edema, were recorded. Serious adverse events were defined as any event requiring care at the emergency department or hospital admission.

### Study outcome

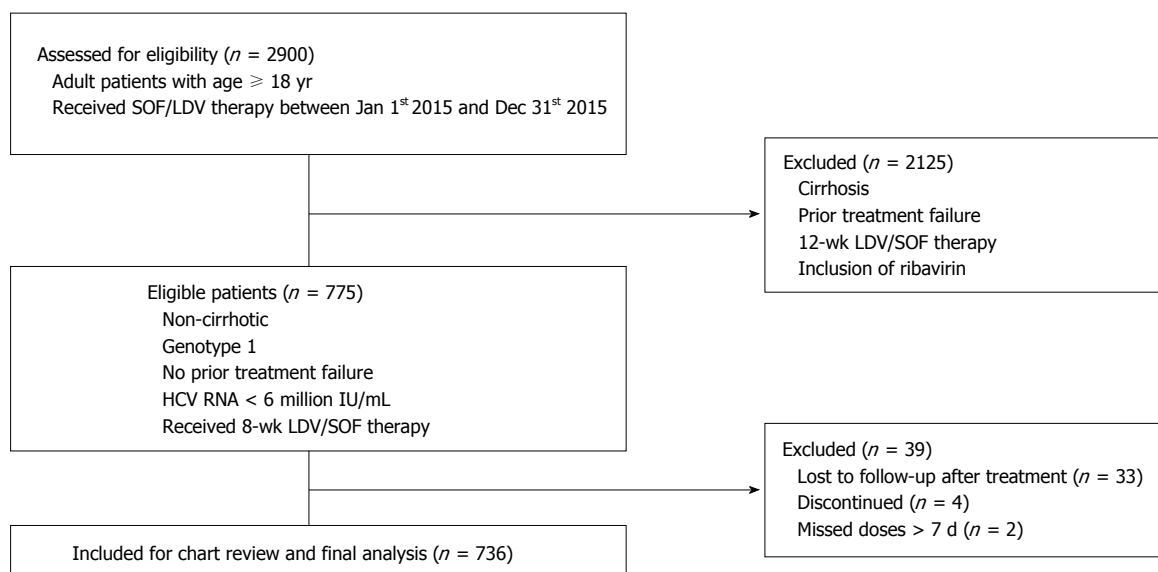
Primary outcome of our study was achievement of SVR at 12 wk after treatment. Secondary outcomes were identifying predictors of treatment failure and adverse events during treatment. SVR was defined as non-detectable level of HCV-RNA test.

### Statistical analysis

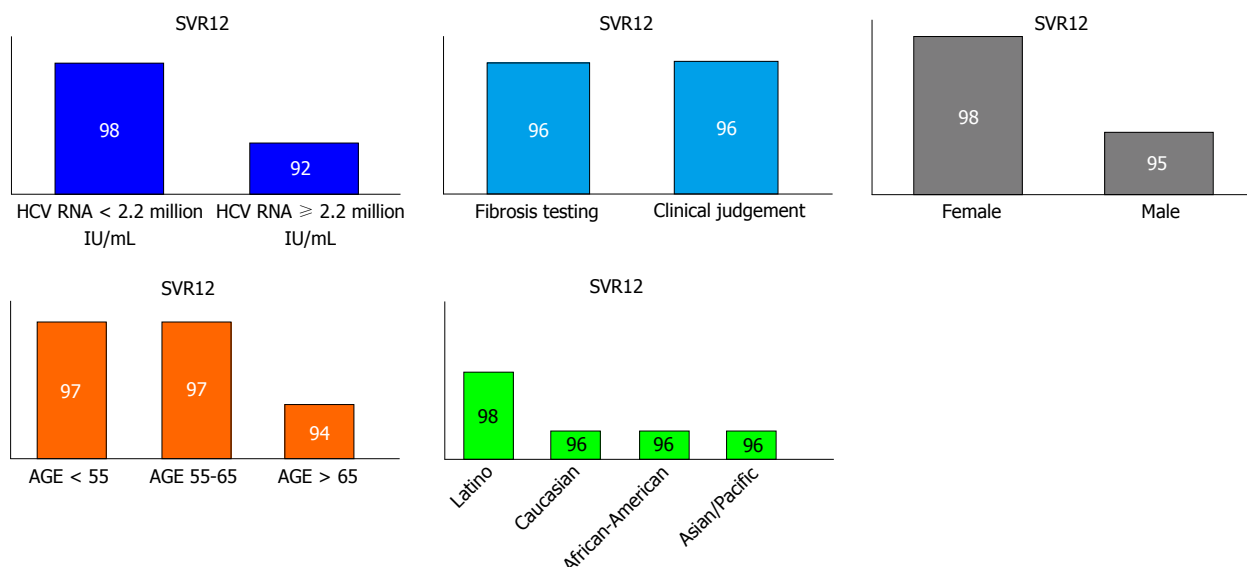
For the primary endpoint evaluating SVR12 and for the evaluation of adherence, the final analysis was restricted to *per-protocol* fashion of those patients who completed therapy and returned for follow-up HCV-RNA testing 3 mo after the end of treatment. The rationale to exclude patients who were lost to follow-up was to counter artificial lowering of the calculated SVR rates. Descriptive statistics were used to compare the baseline differences between those individuals who did or did not achieve SVR12. We used cross-tabulation with Pearson  $\chi^2$  test to determine the significant difference between categorical variables and 2-tailed Independent-samples *t*-test to determine the significant difference between 1 categorical variable and 1 quantitative variable. We used multivariate logistic regression to estimate OR and 95%CI to identify predictors of treatment failure while adjusting for confounding variables. All data were entered into and analyzed using IBM SPSS Statistics 20 (IBM, Armonk, NY, United States).

## RESULTS

We identified total of 775 non-cirrhotic, genotype 1



**Figure 1** Flow chart of patient selection process. This flow chart summarizes patient identification for eligibility and inclusion/exclusion criteria.



**Figure 2** Sustained virologic response rates among patients with various clinical and demographic characteristics. SVR: Sustained viral response.

HCV patients with HCV-RNA < 6 million IU/mL who received 8-wk LDV/SOF treatment. Seven hundred and thirty-six patients were included in the final analysis after exclusion of patients who reported missing doses, discontinued treatment due to adverse events and patients who did not follow-up for SVR12. Figure 1 demonstrates the flow chart of patient selection process.

The demographic and clinical characteristics of patients are outlined in Table 1. The mean age was 58 years, 55% were males, 51% were Caucasian and 65% had genotype 1a infection. Fifty-three percent of patients considered to be non-cirrhotic were determined by healthcare providers based on clinical judgement (platelet count, spleen size, hepatic morphology on ultrasound) and 47% patients had documented liver fibrosis testing (43% liver biopsy, 3%

VCTE and 0.4% FIBROSPECT II). Mean HCV-RNA log<sub>10</sub> was 6.2.

Table 2 demonstrates the study outcomes (SVR). Overall SVR12 was 96%. None of the patients who achieved SVR12 had viral relapse at 24-wk post treatment. Fifty-nine percent patients had SVR24 data at the time of analysis. We found no difference in SVR12 between patients whose non-cirrhotic state was determined by clinical judgment and patients who had fibrosis testing. No significant difference in SVR12 was seen among gender, genotype 1 subtype, ethnicity, type of fibrosis tests and fibrosis stages. Special populations; those co-infected with HIV and HBV achieved 100% SVR12. When reviewed by age groups, patients with age > 65 years had lower SVR compared to age groups 55-65 and < 55 years but no statistical significance was observed (Figure 2).



**Table 1** Demographic and clinical characteristics of patients prior to hepatitis C treatment *n* (%)

Characteristics	<i>n</i> = 736
Age, mean $\pm$ SD (yr)	58 $\pm$ 10
Range	(23-85)
Male sex	403 (55)
Ethnicity	
Caucasian	374 (51)
African American	178 (24)
Hispanic	158 (21)
Asian/Pacific islanders	26 (4)
HCV genotype-subtype	
1a	475 (64)
1b	242 (33)
1 without confirmed subtype	19 (3)
Liver biopsy	317 (43)
Vibration-controlled transient elastography	25 (3)
FIBROSpect II	3 (0.4)
Overall fibrosis score	
Stage 0	45 (13)
Stage 1	164 (48)
Stage 2	104 (30)
Stage 3	29 (8)
Stage 3-4 or 4	2 (1)
Non-cirrhotic state determined by clinical judgement	391 (53)
HCV RNA - log <sub>10</sub> IU/mL, mean $\pm$ SD	6.2 $\pm$ 0.2
HCV RNA $\geq$ 2.2 million IU/mL	219 (30)
Pre-treatment laboratory values	
GFR, mean $\pm$ SD (Range)	79 $\pm$ 11 (40-89)
Platelet count (10 <sup>3</sup> /mm <sup>3</sup> ), mean $\pm$ SD (Range)	218 $\pm$ 55 (45-495)
INR, mean $\pm$ SD (Range)	0.99 $\pm$ 0.7 (0.8-1.3)
Albumin, mean $\pm$ SD (Range)	3.9 $\pm$ 0.4 (2.1-5.1)
Missing	101 (14.0)
Co-morbid conditions	
Psychiatric diagnoses	145 (20.0)
Chronic kidney disease	35 (5.0)
Psoriasis	16 (2.0)
HIV co-infection	5 (0.7)
Cryoglobulinemia	4 (0.5)
HCV-related glomerulonephritis	2 (0.3)
HBV co-infection	2 (0.3)
Hepatocellular carcinoma	1 (0.1)

HCV: Hepatitis C virus; HBV: Hepatitis B virus; GFR: Glomerular filtration rate; INR: International normalized ration; HIV: Human immunodeficiency virus.

We found that HCV RNA viral load plays a role in predicting SVR with high accuracy - the area under a receiver operating characteristic (AUROC) was 0.743 (95%CI: 0.66-0.82) with a cutoff value of 2.2 million IU/mL, as depicted in Figure 3. A significantly lower SVR was observed among patients with HCV-RNA more than 2.2 million IU/mL (91% vs 98%,  $P < 0.001$ ). Table 3 exhibits the odds ratios for SVR12 in multivariate logistic regression. We found that patients with HCV-RNA less than 2.2 million IU/mL were more likely to achieve SVR compared to those with more than 2.2 million IU/mL (OR = 0.22, 95%CI: 0.1-0.49,  $P < 0.001$ ). Age groups, gender, ethnicity and genotype 1 subtype did not predict SVR. Non-cirrhotic state determined by clinical judgment based on simple, non-invasive tests was not associated with lower SVR (OR = 1.02, 95%CI: 0.48-2.17,  $P = 0.962$ ).

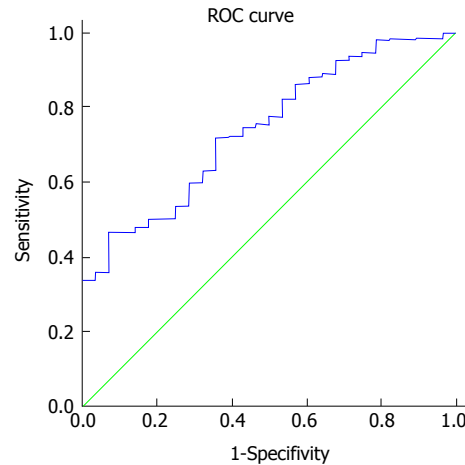
**Figure 3** Area under a receiver operating characteristic curve for hepatitis C RNA viral load was 0.734 ( $P < 0.001$ , 95%CI: 0.66-0.82).

Table 4 reveals the safety analysis of the patients who received 8-wk LDV/SOF therapy. Three (0.5%) patients discontinued treatment due to intolerable adverse events: severe rheumatoid arthritis exacerbation, intractable nausea and declining renal function with glomerular filtration rate 22. One patient who developed drug-induced liver injury (DILI) from LED/SOF therapy with positive biopsy findings discontinued the treatment. Interestingly, one of two patients who were excluded from the study due to missing more than 7 d of therapy achieved SVR. This patient HCV-RNA was 625000 IU/mL. No death or significant morbidities were reported. Four (0.5%) patients experienced serious adverse events during therapy: 2 were hospitalized for observation to evaluate non-cardiac chest pain, 1 was hospitalized for DILI and 1 was due to emergency department admission for pneumonia. The most common minor adverse events were fatigue (14%), headache (13%), insomnia (5%), arthralgia/myalgia (4%) and nausea (4%).

## DISCUSSION

Our findings have validated that SVR rate of 8-wk LDV/SOF therapy in treatment naïve, non-cirrhotic, genotype 1 HCV patients with RNA  $< 6$  million IU/mL is comparable with clinical trials and preliminary outcomes from small real-world studies<sup>[7-9]</sup>. We demonstrated that there is no difference in SVR between patients whose cirrhosis state was determined by fibrosis testing or clinical judgment. All patients had at least baseline ultrasound of the liver and blood tests such as transaminases levels, platelet count and International normalized ration. We calculated overall fibrosis stages on biopsy, VCTE and FIBROSPECT II and found no difference in SVR across fibrosis stages although very few patients had stage 0, 3 and 4. Our finding suggests that clinical judgment of non-cirrhotic state results in same outcome of SVR 96% compared to SVR of patients who had liver biopsy, VCTE or FIBROSPECT

**Table 2** Sustained viral response 12 rate by various patient characteristics for non-cirrhotic patients with genotype 1 hepatitis C virus infection treated with 8-week ledipasvir/sofosbuvir therapy

Characteristics	SVR12 (%) (n = 736)	P value
Overall	96 (708/736)	
Non-cirrhotic state determined by clinical judgement	96 (376/391)	0.962
Non-cirrhotic state determined by biopsy, VCTE, FIBROSPECT II	96 (332/345)	
HCV RNA $\geq$ 2.2 million IU/mL	92 (201/219)	< 0.001
HCV RNA < 2.2 million IU/mL	98 (507/270)	
HIV co-infection	100 (6/6)	
HBV co-infection	100 (2/2)	
Gender		0.071
Male	95 (383/403)	
Female	98 (325/333)	
HCV genotype-subtype		0.414
1a	96 (454/475)	
1b	98 (236/324)	
Undetermined	95 (18/19)	
Ethnicity		
Caucasian	96 (357/374)	
African American	96 (171/178)	
Hispanic	98 (155/158)	0.544
Asian/Pacific Islander	96 (25/26)	
Age groups		0.311
< 55 yr	97 (216/223)	
55-65 yr	97 (369/382)	
> 65 yr	94 (123/131)	
Fibrosis Tests		0.489
Liver biopsy	97 (306/317)	
Vibration-controlled transient elastography	92 (23/25)	
FIBROSPECT II	100 (3/3)	
Overall fibrosis stage (cumulative: biopsy/VCTE/FIBROSPECT II)		
Stage 0	98 (44/45)	
Stage 1	95 (155/164)	0.611
Stage 2	98 (102/104)	
Stage 3	97 (28/29)	
Stage 4	100 (2/2)	

HCV: Hepatitis C virus; VCTE: Vibration-controlled transient elastography; SVR: Sustained viral response.

**Table 3** Odds ratios for sustained viral response at 12 week in multivariate logistic regression for non-cirrhotic, hepatitis c genotype 1 patients treated with 8-week ledipasvir/sofosbuvir therapy

Characteristics	OR (95%CI) for SVR12 (n = 736)	P value
Age 55-65 yr (ref. < 55)	0.92 (0.36-2.34)	0.861
Age > 65 yr (ref. < 55)	0.5 (0.18-1.41)	0.188
Male (ref. female)	0.47 (0.21-1.08)	0.077
African-American (ref. Caucasian)	0.84 (0.11-6.57)	0.868
Hispanic (ref. Caucasian)	2.07 (0.21-20.66)	0.537
Asian/Pacific Islander (ref. Caucasian)	0.98 (0.16-8.28)	0.983
Non-cirrhotic state determined by clinical judgement (ref. Fibrosis Test: biopsy/VCTE/FIBROSPECT)	1.02 (0.48-2.17)	0.962
HCV RNA $\geq$ 2200000 IU/mL (ref. < 2200000 IU/mL)	0.22 (0.1-0.49)	< 0.001
HCV genotype - subtype 1b (ref. 1a)	2.19 (0.25-19.15)	0.480

HCV: Hepatitis C virus; VCTE: Vibration-controlled transient elastography; SVR: Sustained viral response.

tests.

In our cohort, all patients had pre-treatment HCV-RNA < 6 million IU/mL. We divided to 2 subgroups containing RNA < 800000 IU/mL and > 800000 IU/mL. We found that patients with lower RNA < 800000 IU/mL achieved significantly higher SVR compared to patients with higher RNA in both univariate and multivariate analyses. This finding suggests that HCV viral load plays an important role in predicting SVR

although the determination of the optimal cut-off value of HCV-RNA level to consider 8-wk therapy to achieve SVR is currently not available<sup>[14]</sup>. Our study highlights that HCV RNA 2.2 million IU/mL was associated significant impact on outcomes with AUROC 0.73. While female gender and Latino ethnicity achieved slightly higher SVRs, there is no statistical difference compared to male gender and other ethnicities. We found no difference in SVR rates between African-

**Table 4** Adverse events, hospital admissions and discontinuation rates of patients with genotype 1 hepatitis C virus infection who received 8-wk ledipasvir/sofosbuvir therapy

Adverse events	n (%)
No. adverse event, mean $\pm$ SD (Range)	0.5 $\pm$ 0.7 (0-6)
Serious adverse events	4 (0.5)
Hospital admissions	
Non-cardiac chest pain	2
Drug-induced liver injury	1
Pneumonia	1
Minor adverse events	
Fatigue	104 (14)
Headache	98 (13)
Insomnia	35 (5)
Arthralgia/myalgia	29 (4)
Nausea	29 (4)
Cough	15 (2)
Rash	19 (3)
Dizziness	12 (2)
Diarrhea	14 (2)
Pruritus	11 (1)
Irritability/anxiety	10 (1)
Edema	2 (< 0.5)
Discontinuation	4 (0.5)
Drug-induced liver injury	1
Severe rheumatoid arthritis exacerbation	1
Intractable nausea	1
Decreased renal function during treatment (GFR < 30)	1
Death	0

GFR: Glomerular filtration rate.

Americans and Caucasians in contrast to other studies which demonstrated the decreased likelihood of SVR in African-American population<sup>[12]</sup>.

The wholesale acquisition cost for LDV/SOF combination drug in the United States is \$1125 per pill. Cost of 8-wk course of therapy is \$63000 and cost of 12-wk course is \$94500 - net cost saving of \$31500 per patient when 8-wk treatment is administered. Healthcare expenses can substantially be reduced by selecting 8-wk LDV/SOF therapy in treatment-naïve, non-cirrhotic genotype 1 HCV patients.

The strengths of our study are its real-world experience and an integrated healthcare model involving all clinical services. We were able to abstract data regarding all clinic/emergency department/urgent care visits, hospitalizations, telephone/electronic-mail encounters and all laboratory tests from the integrated EMR system. All providers used KPSC-Regional HCV treatment guidelines which is readily available on the EMR system for review. Treatment duration, reasons for discontinuation and medication compliance were clearly documented. All patients in the final analysis had good post-treatment follow ups with available SVR12 data. The limitation of our study is its retrospective nature.

In conclusion, our outcomes from real-world cohort validate high SVR rates in non-cirrhotic, treatment naïve HCV genotype 1 patients with HCV RNA < 6 million IU/mL who received 8-wk LDV/SOF therapy. There was no difference in SVR between patients

whose non-cirrhotic state was determined by clinical judgment and patients who had fibrosis testing. HCV RNA less than 2.2 million IU/mL was associated with significantly higher SVR. LDV/SOF therapy is safe and well-tolerated with high adherence rates. Therefore, 8-wk LDV/SOF therapy can be used in selected subset of patients with chronic HCV genotype 1 infection who meet aforementioned clinical criteria. Further studies are in need to evaluate and validate HCV RNA cutoff value to achieve the optimal more than 95% of SVR.

## COMMENTS

### Background

Hepatitis C treatment has evolved from a 78-wk interferon monotherapy to 48-wk pegylated interferon plus ribavirin therapy and now 12-wk therapy with newer all-oral direct-acting antiviral (DAA) agents. DAA regimens have revolutionized the treatment of hepatitis C with their excellent sustained virologic response (SVR), tolerable side effect profiles and shorter duration of therapy. Although ION-3 trials and other real-world studies have revealed that 8-wk ledipasvir/sofosbuvir therapy is effective and has comparable sustained viral response outcomes for non-cirrhotic patients who have untreated genotype-1 hepatitis C virus (HCV) infection and HCV RNA < 6 million IU/mL, the current AASLD guidelines recommend 12-wk therapy. Eight-week therapy may provide significantly lower cost, better patient compliance and adherence.

### Research frontiers

The authors validated that SVR outcomes in 8-wk LED/SOF therapy was comparable with 12-wk therapy in this large, real-world cohort.

### Innovations and breakthroughs

This study highlights that HCV RNA 2.2 million IU/mL was associated significant impact on outcomes with AUROC 0.73. Patients with HCV RNA more than 2.2 million IU/mL were observed to have significantly lower SVR (92% vs 98%,  $P < 0.001$ ). They found no difference in SVR rates between African-Americans and Caucasians in contrast to other studies which demonstrated the decreased likelihood of SVR in African-American population.

### Applications

This study validate other real-world studies which have shown that 8-wk therapy in selected subset of patients (non-cirrhotic, untreated, genotype-1 with HCV RNA < 6 million IU/mL) is effective and comparable to 12-wk therapy. We can apply these findings and amend changes in national guidelines regarding HCV treatment which can save significant amount of HCV treatment cost and boost patient compliance and adherence.

### Peer-review

This study is good, and it's important knowledge for clinicians before treating HCV patients.

## REFERENCES

- 1 **Rosen HR.** Clinical practice. Chronic hepatitis C infection. *N Engl J Med* 2011; **364**: 2429-2438 [PMID: 21696309 DOI: 10.1056/NEJMcpl006613]
- 2 **Denniston MM,** Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014; **160**: 293-300 [PMID: 24737271 DOI: 10.7326/M13-1133]
- 3 **Edlin BR,** Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology* 2015; **62**: 1353-1363 [PMID: 26171595 DOI: 10.1002/hep.27978]
- 4 **Jacobson IM,** Davis GL, El-Serag H, Negro F, Trépo C. Prevalence

- and challenges of liver diseases in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol* 2010; **8**: 924-933; quiz e117 [PMID: 20713178 DOI: 10.1016/j.cgh.2010.06.032]
- 5 **Chhatwal J**, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med* 2015; **162**: 397-406 [PMID: 25775312 DOI: 10.7326/M14-1336]
  - 6 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]
  - 7 **Lai JB**, Witt MA, Pauly MP, Ready J, Allerton M, Seo S, Witt DJ. Eight- or 12-Week Treatment of Hepatitis C with Ledipasvir/Sofosbuvir: Real-World Experience in a Large Integrated Health System. *Drugs* 2017; **77**: 313-318 [PMID: 28078644 DOI: 10.1007/s40265-016-0684-4]
  - 8 **Kowdley KV**, Sundaram V, Jeon CY, Qureshi K, Latt NL, Sahota A, Lott S, Curry MP, Tsai N, Chaiyakunapruk N, Lee Y, Petersen J, Buggisch P. Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 hepatitis C virus infection. *Hepatology* 2017; **65**: 1094-1103 [PMID: 28027579 DOI: 10.1002/hep.29005]
  - 9 **Backus LI**, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naïve, genotype 1 hepatitis C-infected patients. *Hepatology* 2016; **64**: 405-414 [PMID: 27115523 DOI: 10.1002/hep.28625]
  - 10 **Wilder JM**, Jeffers LJ, Ravendhran N, Shiffman ML, Poulos J, Sulkowski MS, Gitlin N, Workowski K, Zhu Y, Yang JC, Pang PS, McHutchison JG, Muir AJ, Howell C, Kowdley K, Afdhal N, Reddy KR. Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: A retrospective analysis of phase 3 data. *Hepatology* 2016; **63**: 437-444 [PMID: 26547499 DOI: 10.1002/hep.28334]
  - 11 **American Association for the Study of Liver Diseases**; Infectious Diseases Society of America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Available from: URL: <http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection>
  - 12 **European Association for Study of Liver**. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015; **63**: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]
  - 13 Harvoni (ledipasvir and sofosbuvir) tablet product information. Foster City, CA: Gilead Sciences, Inc.; 2015. Available from: URL: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/205834s001lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s001lbl.pdf)
  - 14 **O'Brien TR**, Feld JJ, Kottlilil S, Pfeiffer RM. No scientific basis to restrict 8 weeks of treatment with ledipasvir/sofosbuvir to patients with hepatitis C virus RNA < 6,000,000 IU/mL. *Hepatology* 2016; **63**: 28-30 [PMID: 26474163 DOI: 10.1002/hep.28292]

**P- Reviewer:** Gatselis NK, Ratnasari N, Sirin G **S- Editor:** Gong ZM  
**L- Editor:** A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

