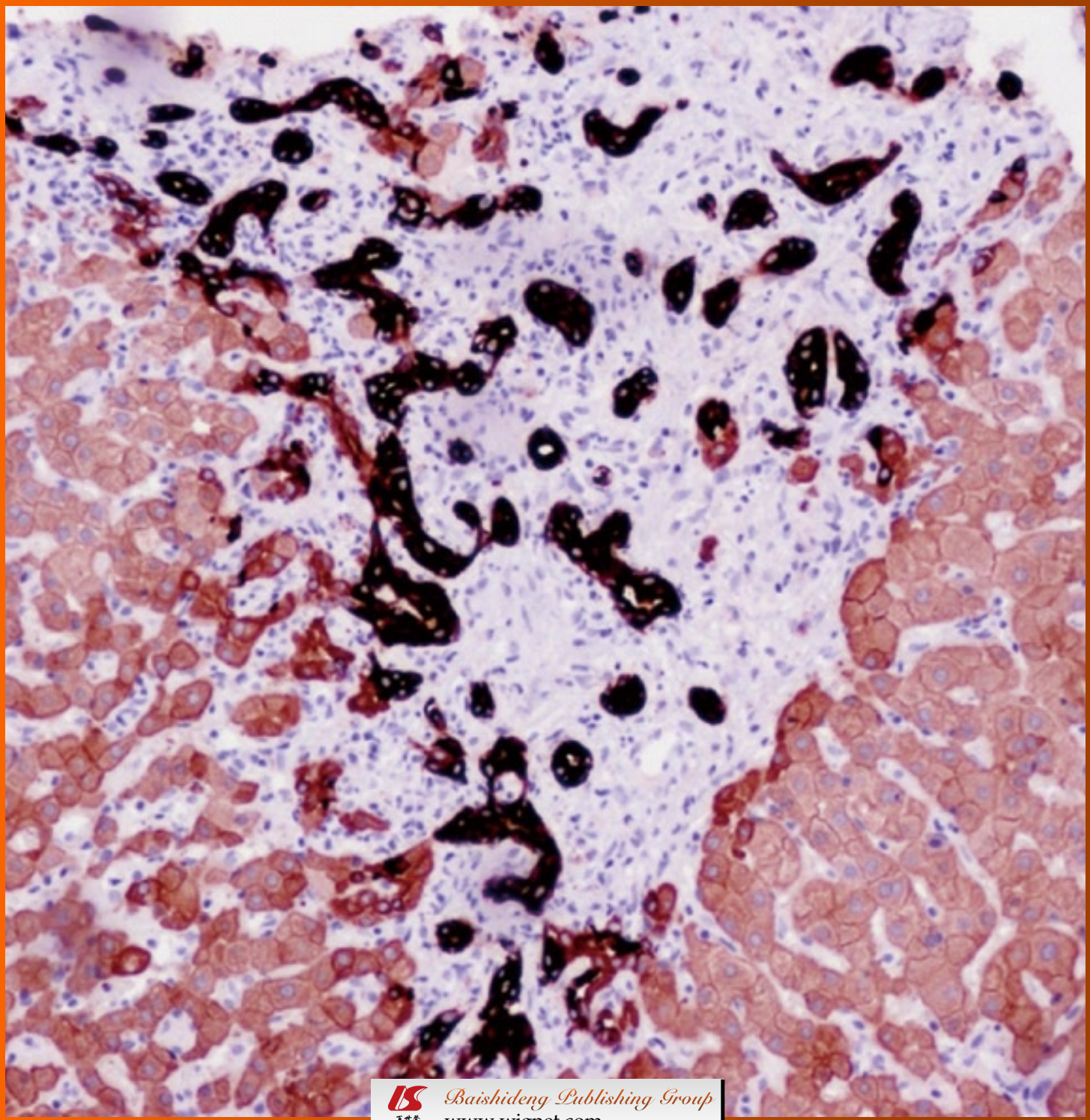
ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2010 November 27; 2(11): 395-418



Baishideng Publishing Group
www.wjgnet.com

WJH World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

Editorial Board

2009-2013

The *World Journal of Hepatology* Editorial Board consists of 572 members, representing a team of worldwide experts in hepatology. They are from 45 countries, including Argentina (4), Australia (7), Austria (2), Bangladesh (1), Belgium (3), Botswana (2), Brazil (8), Brunei Darussalam (1), Bulgaria (1), Canada (10), Chile (1), China (89), Egypt (3), Finland (1), France (15), Gambia (1), Germany (28), Greece (8), Hungary (3), India (20), Ireland (1), Israel (7), Italy (65), Japan (45), Malaysia (1), Mexico (4), Netherlands (4), Pakistan (2), Poland (1), Portugal (1), Philippines (1), Romania (1), Saudi Arabia (1), Singapore (4), South Korea (17), Spain (22), Sri Lanka (1), Sudan (1), Switzerland (2), Thailand (6), Tunisia (2), Turkey (13), United Kingdom (17), United States (144), and Venezuela (1).

PRESIDENT AND EDITOR-IN-CHIEF

Lian-Sheng Ma, *Beijing*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF

Paolo Cabassa, *Brescia*
Cheng-Shyong Chang, *Changhua*
Jing-Gung Chung, *Taichung*
Yi-Ming Chen, *Taipei*
Antonio Craxì, *Palermo*
Moses S Elisaf, *Ioannina*
Fabio Grizzi, *Milan*
Masatoshi Kudo, *Osaka*
Yasuhiro Kuramitsu, *Yamaguchi*
Huan-Yao Lei, *Tainan*
Hsingjin Eugene Liu, *Taipei*
Yasunobu Matsuda, *Niigata City*
Chin-Hsiao Tseng, *Taipei*
Yong Zeng, *Chengdu*

GUEST EDITORIAL BOARD MEMBERS

Yi-Chen Chen, *Taichung*
Tsung-Jung Lin, *Taipei*
Yi-Wen Liu, *Chiayi*
Jen-Leih Wu, *Taipei*
Suh-Ching Yang, *Taipei*

MEMBERS OF THE EDITORIAL BOARD

Argentina

Patricia Cristina Baré, *Buenos Aires*
Maria Cristina Carrillo, *Rosario*
Juan Carlos Perazzo, *Buenos Aires*
Silvia Cristina Sookoian, *Buenos Aires*

Australia

Anthony S-Y Leong, *Newcastle*
Donald Peter McManus, *Queensland*
Des R Richardson, *New South Wales*
Monica Robotin, *Sydney*
Nathan Subramaniam, *Brisbane*
Nicholas Shackel, *Sydney*
Fiona J Warner, *New South Wales*

Austria

Wolfgang Mikulits, *Vienna*
Lothar Bernd Zimmerhackl, *Innsbruck*

Bangladesh

Mamun Al Mahta, *Banani*

Belgium

Frederik C Berrevoet, *Gent*
Olivier Detry, *Liège*
Philip Meuleman, *Ghent*

Botswana

Francesca Cainelli, *Gaborone*
Sandro Vento, *Gaborone*

Brazil

Niels OS Câmara, *Sao Paulo*
Joel Faintuch, *Sao Paulo*
RCS Ferreira, *Santo Amaro*
Regina CS Godenberg, *Rio de Janeiro*
Cristina Miyazaki, *Rio Preto*
CPMS Oliveira, *Sao Paulo*
MAF Ribeiro JR, *Parnaiba*
Mauricio Silva, *Rio Grande*

Brunei Darussalam

Vui Heng Chong, *Bandar Seri Begawan*

Bulgaria

Nikolai Vasilev Belev, *Plovdiv*

Canada

Vasu D Appanna, *Ontario*
Elijah Dixon, *Alberta*
Fernando Alvarez, *Quebec*
Seyed Ali Gaskari, *Calgary*
Serge Jothy, *Toronto*
Jennifer Linchee Kuk, *Toronto*
Qiang Liu, *Saskatchewan*
Eberhard L Renner, *Toronto*
Eldon A Shaffer, *Alberta*
George Therapondos, *Ontario*

Chile

Luis A Videla, *Santiago*

China

Peng Bing, MD, *Chengdu*

Chiranjib Chakraborty, *Beijing*
Stephen Lam Chan, *Hong Kong*
George G Chen, *Hong Kong*
Min-Shan Chen, *Guangzhou*
Yang Cheng, *Shanghai*
Siu Tim Cheung, *Hong Kong*
Thomas YC Cheung, *Hong Kong*
Yick-Pang Ching, *Hong Kang*
William Chi-shing Cho, *Hong Kong*
Chui Chung-hin, *Hong Kong*
Shuang-Suo Dang, *Xi'an*
Yi-Tao Ding, *Nanjing*
Jian-Gao Fan, *Shanghai*
Yuen Man Fung, *Hong Kang*
Zuo-Jiong Gong, *Wuhan*
Tian-Quan Han, *Shanghai*
Jin-Yang He, *Guangzhou*
Garrett CL Ho, *Hong Kong*
Ji-Ming Hu, *Wuhan*
Can-Hua Huang, *Chengdu*
Zhi-Yong Huang, *Wuhan*
Jian-Hui Jiang, *Changsha*
Dong-Yan Jin, *Hong Kong*
Hsiang-Fu Kung, *Hong Kong*
Lai PBS Lai, *Hong Kong*
Wan YJ Lau, *Hong Kong*
Nancy WY Leung, *Hong Kong*
Jin-Qing Li, *Guangzhou*
Li-Ying Li, *Beijing*
Shu-Chen Li, *Harbin*
Xin-Wei Li, *Shanghai*
Yu-Yuan Li, *Guangzhou*
En-Qi Liu, *Xi'an*
Yin-Kun Liu, *Shanghai*
Chung-Mau Lo, *Hong Kong*
Lun-Gen Lu, *Shanghai*
Ming-De Lu, *Guangzhou*
John M Luk, *Hong Kong*
Guang-Hua Luo, *Changzhou*
Shuang Mei, *Shanghai*
Kelvin KC Ng, *Hong Kong*
Qin Ning, *Wuhan*
Qin Pan, *Shanghai*
Qi-Jun Qian, *Shanghai*
Jian-Min Qin, *Shanghai*
Xian-Jun Qu, *Jinan*
Xue-Ying Sun, *Harbin*
Qin Su, *Beijing*
Wu-Yi Sun, *Hefei*
Hui-Ru Tang, *Wuhan*
Peng Tao, *Nanning*
Eric WC Tse, *Hong Kong*
Bin Wang, Weifang
Xiao-Zhong Wang, *Fuzhou*
Xiu-Jie Wang, *Chengdu*
Zhen-Xia Wang, *Huhhot*
Grace LH Wong, *Hong Kong*
Nathalie Wong, *Hong Kong*
Xiong-Zhi Wu, *Tianjin*
De-Xiang Xu, *Hefei*
Rui-An Xu, *Quanzhou*
Xun-Di Xu, *Changsha*
Xiao Yang, *Beijing*
Zhen-Fan Yang, *Hong Kong*
Boon Hun Yong, *Hong Kong*
Ting-He Yu, *Chengdu*
Benny CY Zee, *Hong Kong*
Jia-Ning Zhang, *Dalian*
Xiao-Dong Zhang, *Tianjin*
Xiao-Lan Zhang, *Shijiazhuang*
Xiao-Yan Zhang, *Shanghai*
Hong-Chuan Zhao, *Hefei*
Xiao-Ping Zhao, *Beijing*
Jiang-Fan Zhu, *Shanghai*
Yi-Ping Zou, *Beijing*

Egypt

Nabil Mohie Abdel-Hamid, *Minia*
Laila AF Eissa, *Mansoura*
Mona Mostafa Fahmy Nosseir, *Giza*

Finland

Thomas Kietzmann, *Oulu*

France

Aramando Abergel, *Clenmont -Ferrant*
Henri Bismuth, *Villejuif Cedex*
Ana CFN Cardoso, *Paris*
Nicolas Chignard, *Paris*
Claude C de Fromentel, *Lyon*
Zdenko Herceg, *Lyon*
Nathalie Janel, *Paris*
Victor de Ledinghen, *Pessac cedex*
Antoinette Lemoine, *Villejuif*
Marcellin Patrick, *Clichy*
Raoul Poupon, *Paris*
Rodrigue Rossignol, *Bordeaux cedex*
Christian Trépo, *Lyon*
Dominique A Vuitton, *Besancon*
Virginie Wautot, *Pierre Benite*

Gambia

Maimuna Ebirunkeh Mendy, *Banjul*

Germany

Thomas Bock, *Tuebingen*
Ali Canbay, *Essen*
Enrico Narciso De Toni, *München*
Joachim Drevs, *Freiburg*
Volker Fendrich, *Marburg*
Peter R Galle, *Mainz*
Erich Gulbins, *Essen*
Roland Kaufmann, *Jena*
Sebastian Hinz, *Kiel*
Philipp Kobbe, *Aachen*
Michael Kremer, *Heidelberg*
Christian Liedtke, *Aachen*
Martin Loss, *Regensburg*
Arun Kumar Mankan, *Munich*
Lars Müller, *MD, Kiel*
Michael D Menger, *Saarbrucken*
Andreas K Nussler, *Munich*
Margarete Odenthal, *Koeln*
Claus Petersen, *Hannover*
Andrej Potthoff, *Hannover*
Thomas Pusl, *München*
Elke Roeb, *Giessen*
Frank Tacke, *Aachen*
Stefan Rose-John, *Kiel*
Andreas Teufel, *Mainz*
Lothar Thomas, *Frankfurt*
Jens JW Tischendorf, *Aachen*
Arndt Vogel, *Hannover*

Greece

Alex P Betrosian, *Athens*
Spiros G Delis, *Athens*
Ioannis Diamantis, *Athens*
Papandreou Dimitrios, *Mela*
Elias A Kouroumalis, *Crete*
George Papatheodoridis, *Athens*
Stamatios E. Theocharis, *Athens*

Hungary

Gábor Bánhegyi, *Budapest*
Subhamay Ghosh, *Pécs*
Peter Nagy, *Budapest*

India

Anjali Deepak Amarapurkar, *Mumbai*
DN Amararpurkar, *Mumbai*
Runu Chakravarty, *Kolkata*
Pronobesh Chattopadhyay, *Moradabad*
Puneet Chopra, *Gurgaon Haryana*
Tanya Das, *Kolkata*
Radha Krishan Dhiman, *Chandigarh*
Ajay Duseja, *Chandigarh*
Devendra K Gupta, *New Delhi*
P Kar, *New Delhi*
Sudhir Kumar, *Lucknow*
Vijay Kumar, *New Delhi*
Anoop Misra, *New Delhi*
Devendra Parmar, *Lucknow*
Rajendra Prasad, *Chandigarh*
K Rajeshwari, *New Delhi*
Pallu Reddanna, *Hyderabad*
Barjesh Chander Sharma, *New Delhi*
Sarman Singh, *New Delhi*
Ajith TA, *Thrissur*

Ireland

Matthew William Lawless, *Dublin*

Israel

Yaron Ilan, *Jerusalem*
Yaakov Maor Kendler, *Tel Hashomer*
Ran Oren, MD, *Tel Aviv*
Amir Shlomai, *Modiin*
Rifaat Safadi, *Jerusalem*
Shira Zelber Sagi, *Tel Aviv*
Yehuda Julius Shoenfeld, *Tel Hahsomer*

Italy

Luca Aasaloni, *Bologna*
Giovanni Addolorato, *Rome*
Luigi E Adinolfi, *Naples*
Pietro Andreone, *Bologna*
M Appetecchia, *Rome*
Antonio Ascione, *Napoli*
Ferruccio Bonino, *Milano*
Bruno D Bruno, *Benevento*
Savino Bruno, *Milano*
Melchiorre Cervello, *Palermo*
Claudio Chiesa, *Rome*
Stefano Colagrande, *Firenze*
Massimo G Colombo, *Milan*
Samuele De Minicis, *Montegranaro*
Alessandro Vitale, *alessandro*
Fabio Farinati, *Padova*
Paolo Feltracco, *Padova*
Domenico Ferri, *Bari*
Amalia Gastaldelli, *Pisa*
Domenico Girelli, *Verona*
Fernando Goglia, *Benevento*
Alessandro Grasso, *Savona*
Ignazio Grattagliano, *Bari*
Pietro Invernizzi, *Milan*
Francesco Izzo, *Naples*
Amedeo Lonardo, *Modena*
Malaguarnera Lucia, *Trecastagni*
Massimo Di Maio, *Rossano*
Melania Manco, *Rome*
Andrea Mancuso, *Palermo*
F Marotta, *Milano*
Fabio Marra, *Florence*
Roberto Mazzanti, *Florence*
Giulia Morsica, *Milan*
Antonio Moschetta, *Bari*
Massimo Negrini, *Ferrara*
Andrea Nicolini, *Pisa*
Giuseppe R Nigri, *Rome*
Valerio Nobili, *Rome*
Valentina Pallottini, *Rome*
Adriano M Pellicelli, *Rome*
Marcello Persico, *Naples*
Massimo Pinzani, *Firenze*
Giovanni Polimeni, *Messina*
Camillo Porta, *Pavia*
Piero Portincasa, *Bari*
Emilio Quaia, *Trieste*
Giuseppe Remuzzi, *Bergamo*
Domenico Ribatti, *Bari*
Massimo Roncalli, *Rozzano*
Carlo Sabbà, *Bari*
Orazio Schillaci, *Rome*
Gaetano Serviddio, *Foggia*
Aurelio Sonzogni, *Bergamo*
Paolo Sorrentino, *Salerno*
Enea Spada, *Roma*
Giovanni Tarantino, *Naples*
Luciano Tarantino, *Naples*
Claudio Tiribelli, *Trieste*
Pierluigi Toniutto, *Udine*
Pietro Vajro, *Naples*
Luca Vigano, *Torino*

Japan

Yuichiro Eguchi, *Saga*
Munechika Enjoji, *Fukuoka*
Jiro Fujimoto, *Osaka*
Atsushi Hosui, *Osaka*
Kazuo Ikeda, *Nagoya*
Toru Ishikawa, *Niigata*
Yoshiaki Iwasaki, *Okayama*
Satoru Kakizaki, *Gunma*
Naoya Kato, *Tokyo*
Takumi Kawaguchi, *Kurume*
Kiminori Kimura, *Tokyo*
Tsuneo Kitamura, *Chiba*
Keiichi Kubota, *Tochigi*
Sabina Mahmood, *Okayama*
Hitoshi Maruyama, *Chiba*
Sachiko Matsuhashi, *Saga*
Toshihiro Mitaka, *Sapporo*
Eiji Miyoshi, *Yamada-oka Suita*
Zenichi Morise, *Toyoake Aichi*
Ryuichi Morisihita, *Osaka*
Yoshiki Murakami, *Kyoto*
Satoru Murata, *Tokyo*
Atsushi Nakajima, *Kanagawa*
Yasuni Nakanuma, *Kanazawa*
Waka Ohishi, *Hiroshima*
Morikazu Onji, *Matsuyama*
Toshiji Saibara, *Nankoku*
Hiroaki Shiba, *Tokyo*
Ikuo Shoji, *Hyogo*
Ryo Sudo, *Yokohama*
Yoshio Sumida, *Nara*
Shinji Tanaka, *Tokyo*
Takuji Tanaka, *Gifu*
Akihiko Tsuchida, *Tokyo*
Takato Ueno, *Kurume*
Shinichi Ueno, *Kagoshima*
Kiyohito Yagi, *Osaka*
Yo-ichi Yamashita, *Hiroshima*
Teruyoshi Yanagita, *Saga*
Shuang-Qin Yi, *Kanazawa*
Hiroshi Yoshida, *Tokyo*
Hitoshi Yoshiji, *Nara*

Malaysia

Kamsiah Jaarin, *Kuala Lumpur*

Mexico

Norberto C Chavez-Tapia, *Tlalpan*
Javier Lizardi Cervera, *Tlalpan CP*
Saúl Villa-Treviño, *México DF*
Florencia V Vorackova, *México DF*

Netherlands

Robert Jacobus de Knegt, *Rotterdam*
TU Hoogenraad, *Heidelberglaan*
Maarten E Tushuizen, *MB Amsterdam*
Robert C Verdonk, *RB Groningen*

Pakistan

Syed Hamid Ali, *Karachi*
Huma IQ TI, *Islamabad*

Poland

Maria ES Lotowska, *Bialystok*

Portugal

Felix Dias Carvalho, *Porto*

Philippines

Janus P Ong, *Manila*

Romania

Eugen Georgescu, *Craiova*

Saudi Arabia

Ahmed Helmy, *Riyadh*

Singapore

Wei Ning Chen, *Singapore*
Si-Shen Feng, *Singapore*
Lang Zhuo, *Singapore*
Chun-Tao Wai, *Singapore*

South Korea

Sang Hoon Ahn, *Seoul*
Sun Pyo Hong, *Yongin*
Byung Ihn Choi, *Seoul*
Seok Joo Han, *Seoul*
Kyung Lib Jang, *Busan*
Bum-Joon Kim, *Seoul*
Dong Goo Kim, *Seoul*
Kyung Sik Kim, *Seoul*
Meehyein Kim, *Yongin*
Young Chul Kim, *Seoul*
Mi-Kyung Lee, *Jeonnam*
Young-Ik Lee, *Taejon*
Kwan-Kyu Park, *Daegu*
Hyunchul Rhim, *Seoul*
In Kyoung Lim, *Gyunggi-do*
Dae-Yeul Yu, *Daejeon*
Jong Won Yun, *Kyungbuk*

Spain

Jose AG Agundez, *Badajoz*
Maria Angeles, *Madrid*
Agustin Castiella, *Mendaro*
Ruben Ciria, *Cordoba*
Joan Clari, *Barcelona*
Maria Buti Ferret, *Barcelona*

Puri Fortes, *Pamplona*
Joan Genescà, *Barcelona*
María J Gómez-Lechón, *Valencia*
Arias Jaime, *Madrid*
Ángeles Pajares María, *Madrid*
Jordi Muntane, *Cordoba*
Jose JG Marin, *Salamanca*
Julia P Onsurbe, *Barcelona*
Albert Parés, *Barcelona*
Sonia Ramos, *Madrid*
Cristina Ripoll, *Madrid*
Isabel F Romero, *Barcelona*
Marta R Romero, *Salamanca*
Juan Macias Sanchez, *Sevilla*
Juan Sastre, *Valencia*
Manuel Vázquez-Carrera, *Barcelona*

Sri Lanka

EGD Shaman Rajindrajith, *Ragama*

Sudan

Hatim MY Mudawi, *Khartoum*

Switzerland

Beat Mullhaupt, *Zurich*
Maurer A Christoph, *Liestal*

Thailand

Nattiya Hirankarn, *Bangkok*
Somchai Pinlaor, *Khon Kaen*
Yong Poovorawan, *Bangkok*
Abhasnee Sobhonslidsuk, *Bangkok*
Chanitra Thuwajit, *Bangkok*
Sopit Wongkham, *Khon Kaen*

Tunisia

Olfa Bahri, *Tunis-Belvedere*
Chadli Dziri, *Tunis*

Turkey

Inci Alican, *Istanbul*
Ahmet Atessahin, *Elazig*
Yasemin Hatice Balaban, *Ankara*
Hayrullah Derici, MD, *Izmir*
Cigdem Ulukaya Durakbasa, *Istanbul*
Muhsin MM Harputluoglu, *Malatya*
Abdurrahman Kadayifci, *Gaziantep*
Adnan Kadayifci, *Antalya*
Ali Sazci, *Kocaeli*
Ilker Tasci, *Ankara*
Mehmet Yalniz, *Elazig*
Serkan Yener, *Izmir*
Yusuf Yilmaz, *Istanbul*

United Kingdom

Alastair David Burt, *Newcastle*
David O Cosgrove, *London*
Anil Dhawan, *London*
Indra Neil Guha, *Nottingham*
Phillip M Harrison, *London*
Hübscher SG Hübscher, *Birmingham*
Long R Jiao, *London*
AT Koulaouzidis, *Edinburgh*
Patricia Lalor, *Birmingham*
David A Lomas, *Cambridge*
Rajeshwar P Mookerjee, *London*
Gareth J Morris-Stiff, *Wales*
Kathryn L Nash, *Southampton*
Derek Anthony O'Reilly,
Christian P Selinge, *Bolton*
Konstantinos Tziomalos, *London*
Feng Wu, *Oxford*

United States

Gary A Abrams, *Montgomery*
Hassan H A-Kader, *Tucson*
Hans-Olov Adami, *Massachusetts*
Joseph Ahn, *Maywood*
Shannon Marie Bailey, *Alabama*
Numan Cem Balci, *St Louis MO*
Edmund J Bini, *New York*
Victor E Buckwold, *Frederick*
Roniel Cabrera, *Gainesville*
Guoqing Cao, *Indiana*
Disaya Chavalitdhamrong, *New York*
Chien-Shing Chen, *Loma Linda*
Fei Chen, *Morgantown*
Su Chen, *San Antonio*
Youhai H Chen, *Philadelphia*
Anne M Covey, *New York*
Mark J Czaja, *New York*
Srikanta Dash, *New Orleans*
Anthony JB Demetris, *Pittsburgh*
Sridevi Devaraj, *California*
Lisa Ross Dixon, *Gainesville*
Terrence M Donohue, *Omaha*
Q Ping Dou, *Detroit*
Murray N Ehrinpreis, *Detroit*
Marwan Ghazi Fakih, *Buffalo*
Shengyun Fang, *Maryland*
Claus J Fimmel, *Illinois*
Robert Anthony Fisher, *Virginia*
Samuel W French, *Torrance*
Phillip A Furman, *Princeton*
M Eric Gershwin, *California*
Jalal K Ghali, *Michigan*
Grace Liejun Guo, *Kansas City*
Dieter Haemmerich, *Charleston*
Young S Hahn, *Charlottesville*
Stephen A Harrison, *Texas*
Dee Harrison-Findik, *Nebraska*
Sidhartha Hazari, *Louisiana*
Thomas S Helling, *Jackson*
Alan W Hemming, *Florida*
Iryna S Hepburn, *Evans*
Ai-Xuan L Holterman, *Chicago*
Ke-Qin Hu, *California*
Guangcun Huang, *Ohio*
Wendong Huang, *California*
Rachel M Hudacko, *New Brunswick*
Michael John Jacobs, *Michigan*
Hartmut W Jaeschke, *Kansas City*
Ravi Jhaveri, *North Carolina*
Lynt B Johnson, *Washington*
Neil Louis Julie, *Bethesda*
Sanjay Kakar, *San Francisco*
Sanjeeva P Kalva, *Boston*
Jing X Kang, *Massachusetts*
Hetal Karsan, *Georgia*
Emmet B Keeffe, *California*
Nancy Ellen Kemeny, *New York*
Andrew Scott Kennedy, *Cary*
Kusum K Kharbanda, *Omaha*
David H Kirn, *California*
Hyam Lerner Leffert, *La Jolla*
Stacee Marie Lerret, *Milwaukee*
Fengzhi Li, *New York*
Wei Li, *Houston*
Shuang Liu, *Indiana*
Su Hao Lo, *Davis*
Daniel G Maluf, *Richmond*
Jose E Manautou, *Storrs*
Richard S Mangus, *Indiana*
Mary Ko Manibusan, *Virginia*
Paul Martin, *Miami,*
Jochen Mattner, *Ohio*
James A McCubrey, *North Carolina*
Valentina Medici, *Sacramento*
George Michalopoulos, *Pittsburgh*
Smruti R Mohanty, *Illinois*
John T Moore, *GlaxoSmithKline*
Ravi Murthy, *Texas*
Laura E Nagy, *Cleveland*
Sagar U Nigwekar, *Rochester*
Eileen M O'Reilly, *New York*
Kevin FS O'Carroll, *Hershey*
Melissa Kay Osborn, *Atlanta*
Helieh Saatara Oz, *Kentucky*
Igor P Pogribny, *Arkansas*
Nicholas C Popescu, *Bethesda Maryland*
Daniel S Pratt, *Boston*
Ratna B Ray, *Louis*
Nancy Reau, *Chicago*
Janardan K Reddy, *Chicago*
Martin J Ronis, *Little Rock*
Phillip Ruiz, *Florida*
Tanios B Saab, *Columbus*
Adnan Said, *Madison*
Neeraj Saxena, *Georgia*
Raymund R Saxena, *Minnesota*
Ann Scheimann, *Baltimore*
Timothy M Schmitt, *Charlottesville*
Bernd Schnabl, *La Jolla*
Kunwar Shailubhai, *Pennsylvania*
Muhammad Y Sheikh, *California*
Perry Shen, *Winston-Salem*
Viji Shridhar, *Rochester*
Shivendra D Shukla, *Missouri*
Ashwani K Singal, *Galveston*
Keshav K Singh, *New York*
Omar Skalli, *Shreveport*
Byoung-Joon Song, *Maryland*
Branko Stefanovic, *Tallahassee*
Stephen Strom, *Pennsylvania*
Xiao Su, *San Francisco*
Wing-Kin Syn, *North Carolina*
Gyongyi Szabo, *Massachusetts*
Shinako Takada, *Houston*
Yueming Tang, *Chicago*
John M Taylor, *Philadelphia*
Swee H The, *Springfield*

Chung-Jyi Tsai, *Lexington*
George P Tuszynski, *Pennsylvania*
Jean-Nicolas Vauthey, *Houston*
Michael E de Vera, *Pennsylvania*
Yu-Jui Yvonne Wan, *Kansas*
Jack R Wands, *Providence*
Hanlin L Wang, *Los Angeles*
Xin Wei Wang, *Maryland*
Wahid Wassef, *Worcester*
Ronald J Wong, *California*
George YH Wu, *Farmington*
Hai-Shan Wu, *New York*
Victor W Xia, *California*
Ximing J Yang, *Chicago*
Matthew M Yeh, *Seattle*
Mei Po Yip, *Seattle*
Min You, *Tampa*
Zobair M Younossi, *Falls Church*
Xiao-Fang Yu, *Maryland*
Yong Yuan, *Plainsboro*
Jian X Zhang, *Charlotte*
Jian-Ying Zhang, *El Paso*
Kezhong Zhang, *Michigan*
Yu-Jing Zhang, *New York*
Yuao Zhu, *Durham*
Saša Živković, *Pittsburgh*
William A Zule, *Research Triangle Park*

Venezuela

Flor Pujol de Freychet, *Caracas*

WJH World Journal of Hepatology

Contents

Monthly Volume 2 Number 11 November 27, 2010

World Journal of Hepatology
Volume 2 Number 11 November 27, 2010

Contents

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Na Liu*
Responsible Electronic Editor: *Na Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*
Responsible Science Editor: *Hai-Ning Zhang*
Proofing Editorial Office Director: *Hai-Ning Zhang*

NAME OF JOURNAL
World Journal of Hepatology

LAUNCH DATE
October 31, 2009

SPONSOR
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
Editorial Board of *World Journal of Hepatology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: 00852-3115-8812
Telephone: 00852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
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

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
November 27, 2010

CSSN
ISSN 1948-5182 (online)

PRESIDENT AND EDITOR-IN-CHIEF
Lian-Sheng Ma, *Beijing*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF
Paolo Cabassa, *Brescia*
Cheng-Shyong Chang, *Changhua*
Jing-Gung Chung, *Taichung*
Yi-Ming Chen, *Taipei*
Antonio Craxì, *Palermo*
Moses S Elisaf, *Ioannina*
Fabio Grizzi, *Milan*
Masatoshi Kudo, *Osaka*
Yasuhiro Kuramitsu, *Yamaguchi*
Huan-Yao Lei, *Tainan*
Hsingjin Eugene Liu, *Taipei*
Yasunobu Matsuda, *Niigata City*
Chin-Hsiao Tseng, *Taipei*
Yong Zeng, *Chengdu*

EDITORIAL OFFICE
Hai-Ning Zhang, Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

COPYRIGHT
© 2010 Baishideng. All rights reserved; no part of this publication may be commercially reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior permission of Baishideng. Authors are required to grant *World Journal of Hepatology* an exclusive license to publish.

SPECIAL STATEMENT
All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm. If you do not have web access please wcontact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1948-5182office

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i11.395

World J Hepatol 2010 November 27; 2(11): 395-400
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

EDITORIAL

A new treatment strategy for acute liver failure

Kazuhiro Kotoh, Masaki Kato, Motoyuki Kohjima, Makoto Nakamuta, Munechika Enjoji

Kazuhiro Kotoh, Masaki Kato, Department of Hepatology and Pancreatology, Kyushu University Hospital, Fukuoka 812-8582, Japan
Motoyuki Kohjima, Makoto Nakamuta, Department of Gastroenterology and Clinical Research Center, Kyushu Medical Center, National Hospital Organization, Fukuoka 810-8563, Japan
Munechika Enjoji, Health Care Center, Fukuoka University, Fukuoka 814-0180, Japan
Author contributions: Kotoh K and Enjoji M drafted the editorial; and all of the authors wrote the final version.
Correspondence to: Kazuhiro Kotoh, MD, Department of Gastroenterology and Clinical Research Center, Kyushu Medical Center, National Hospital Organization, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563,
Japan. kotoh-k@intmed3.med.kyushu-u.ac.jp
Telephone: +81-92-6425282 Fax: +81-92-6425287
Received: July 17, 2010 Revised: October 18, 2010
Accepted: October 25, 2010
Published online: November 27, 2010

Abstract

Acute liver failure (ALF) is a syndrome defined by coa gulopathy and encephalopathy and no effective treat ments have been established, except for liver transplantation. However, considering the limited supply of donors, we should endeavor to prevent the progre ssion of this syndrome in its early stage to improve the prognosis of patients with ALF. Recently, several authors have reported that over-activation of intrahepatic macrophages plays an important role in the progression of ALF and we have developed a new treatment method, transcatheter arterial steroid injection therapy (TASIT), to suppress macrophage activation. We have now used TASIT for 5 years and have found that TASIT is effective for patients with over-activation of macrophages in the liver but not for those with lesser activation of macrophages. Therefore, to identify the most appropriate patients for TASIT, we tried to categorize patients with ALF or acute liver injury according to markers for the degree of intrahepatic macrophage activation. This approach was helpful to select the appropriate treatment including liver transplantation. We believe that it is essential to analyze disease progression in each patient before selecting the most appropriate treatment.

© 2010 Baishideng. All rights reserved.

Key words: Acute liver failure; Steroids; Macrophages; Hepatitis; Ferritin

Peer reviewer: Alex P Betrosian, MD, Third Department of Critical care, Athens University, Evgenidion Hopsital, 20 Papadiamantopoulou Str., Athens 11528, Greece

Kotoh K, Kato M, Kohjima M, Nakamuta M, Enjoji M. A new treatment strategy for acute liver failure. *World J Hepatol* 2010; 2(11): 395-400 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i11/395.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i11.395

INTRODUCTION

Acute liver failure (ALF), characterized by massive necrosis of the liver, is a syndrome defined by the onset of coagulopathy and hepatic encephalopathy and has a mortality rate ranging from 50% to 70%[1-6]. Most patients die of liver failure but some die because of bacterial infection or gastro-intestinal bleeding during the progressive decline in liver function. The prognosis of ALF has not dramatically improved, despite the introduction of supporting treatments such as plasma exchange, dialysis and antibiotics[7-10]. Although liver transplantation is the only effective treatment, it is seldom performed, mainly because of the rapid progression of liver failure and the shortage of donors.

Why has the prognosis of ALF not improved? It may be because the pathogenesis of ALF is poorly understood. With limited understanding of the underlying pathogenesis, we cannot evaluate ways to prevent the progression of liver failure. ALF is considered to be a syndrome, which means that there are various routes that lead to

massive liver necrosis. Therefore, in the past, the possible roles of triggers such as hepatitis viruses and hepatotoxic materials have been extensively discussed. However, none of the underlying mechanisms have been clarified, except in the cases caused by acetaminophen[11-13].

Recently, several authors reported increased serum levels of macrophage-derived factors in patients with ALF, irrespective of the trigger, which suggests that activated macrophages play an important role in the progression of ALF[14-16]. These reports led us to categorize patients with ALF in terms of the relationship between the macrophage activation and disease progression and to develop a new treatment, transcatheter arterial injection therapy (TASIT), for patients in the early stage of ALF. Based on our analyses of the accumulated cases, this treatment has elicited good responses in many patients but specific conditions were required for the responders. In this article, we discuss the clinical usefulness of TASIT and our system to identify patients with ALF/acute liver injury who would likely benefit from TASIT.

ACTIVATED MACROPHAGES AND MICROCIRCULATORY DISTURBANCES

In the last decade, several authors have reported increases in macrophage-derived CD-163 and osteopontin in the serum of patients with ALF[14-16]. Using the hypothesis that these factors might be produced by activated macrophages in the liver, we pathologically examined a series of resected livers from patients with ALF who had undergone liver transplantation and liver biopsy samples from patients in the early stage of ALF with very high levels of serum alanine aminotransferase (ALT)[17]. Of note, we found diffuse proliferation of activated macrophages in the liver in the majority of these resected livers and biopsy samples.

To collect further evidence of macrophage activation, we measured the serum ferritin concentration in 100 patients with severe acute liver injury, including ALF. The etiology of acute liver injury included HAV (n = 9), HBV (n = 31), HCV (n = 3), drugs other than acetaminophen (n = 6), Wilson's disease (n = 5), autoimmune hepatitis (n = 3) and 43 cases with indeterminate etiology. We found that the serum ferritin levels were elevated in most patients and, in about a half of them, the concentrations exceeded 10 000 ng/mL[17]. Although the serum ferritin levels are elevated in various diseases including infectious diseases and malignancies, such markedly high levels are comparable to those found only in macrophage activating syndrome[18-20]. Importantly, in some patients, the serum ferritin concentration was in the normal range or only slightly elevated, despite ALT levels exceeding 1 000 U/L. It is known that the serum ferritin concentration increases in acute hepatitis and that the elevated ferritin is derived from collapsed hepatocytes. However, the presence of patients with high ALT and normal ferritin levels strongly suggests that the remarkably elevated serum ferritin concentration in acute liver injury is mainly derived from activated macrophages and not from hepatocytes[21-26].

Because the activation of macrophages in the liver occurs during the early stage of ALF and worsens liver damage, it remains unclear how the activated macrophages are involved in the massive hepatocytic death. To answer this question, we focused on the production of lactate dehydrogenase (LDH) in the liver which increases in response to hypoxia[27-29]. Pathological examination of liver biopsy samples from patients in the early stage of ALF showed that hepatocytic LDH expression increased in correlation with macrophage proliferation. According to these findings, we believe that the terminal process underlying massive hepatocytic death in ALF might be intrahepatic hypoxia caused by microcirculatory disturbances in the liver. Although the steps involved in the progression from macrophage activation to hepatic microcirculatory disturbances are unclear, it is likely that the macrophages secrete cytokines that harm the endothelial cells, resulting in fibrin accumulation in the sinusoid as revealed in animal models[30].

TRANSCATHETER ARTERIAL STEROID INJECTION THERAPY

If the activation and proliferation of macrophages in the liver are the main causes of the massive hepatocytic death, a procedure that suppresses macrophage activity in patients in the early stage of ALF could prevent progression to severe liver failure. Based on this hypothesis, we developed a new treatment method called TASIT in 2005[31]. In this procedure, methylprednisolone is injected *via* the proper hepatic artery for 2 h (1 000 mg/d for 3 d). If severe coagulopathy is observed, once daily plasma exchange is added to the regimen.

In 2006, we reported our initial results for the first 17 patients who underwent TASIT and evaluated its efficacy and safety by comparison with the same number of patients who were admitted just before the introduction of TASIT or who rejected TASIT[31]. The patients enrolled in that study fulfilled at least one of the following criteria: (1) progressive and sustained prolonged prothrombin time (PT) [PT-international normalized ratio (INR) > 1.5 for 3 d]; (2) presence of ascites; or (3) presence of hepatic encephalopathy. Although the study was not a randomized trial, the prognosis of the patients treated with TASIT was dramatically improved compared with those without TASIT, with survival rates of 76% and 24% respectively. Furthermore, no complications, other than a transient elevation in the serum glucose concentration, were observed. For cases where TASIT was effective, the coagulopathy and encephalopathy improved rapidly (unpublished observations). The average duration of hospitalization for conservative survivors with TASIT was less than 2 wk. To date, a total of 71 patients with ALF or severe acute liver injury expecting to proceed to ALF have undergone TASIT and the conservative survival rate exceeds 70%. We have experienced no complications directly caused by the TASIT procedure except one case in which a limited puncture site hematoma was observed.

To clarify how the arterially injected steroids affect

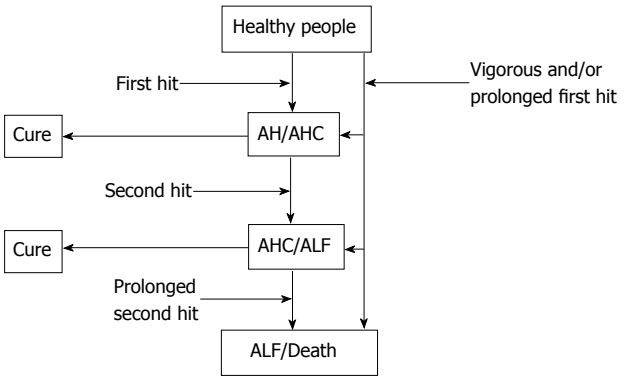


Figure 1 Overview of acute liver failure. Various triggers may directly harm the hepatocytes as a first hit, although this is usually not strong enough to lead to acute liver failure (ALF). In some patients who experience a first hit, over-activation of macrophages occurs in the liver as a second hit which leads to microcirculatory disturbances in the liver and massive hepatocyte death. The activated macrophages spontaneously decline in some patients but, if this activity is prolonged, the risk of death is substantially increased. Overall, the degree of liver damage is determined by the sum of the first and second hit. AH: acute hepatitis; AHC: acute hepatitis with coagulopathy.

the activated macrophages in the liver, we investigated the pathological changes in some patients by comparing liver biopsy samples taken before and 1 wk after TASIT. This study revealed that the number of proliferated macrophages decreased after TASIT, as did LDH production, indicating that the efficacy of TASIT is dependent on correcting intrahepatic microcirculatory disturbances by suppressing macrophage activity.

CLASSIFICATION OF PATIENTS FOR APPROPRIATE TREATMENT

As described above, ALF is defined as a syndrome associated with coagulopathy and hepatic encephalopathy. Several liver-supporting treatments are recommended for patients who fulfilled the criteria of ALF but there are no guidelines for patients with coagulopathy but not encephalopathy. Because the transition from acute liver injury without encephalopathy to ALF is continuous, there are currently no methods to predict the prognosis of patients with severe acute liver injury and the likelihood of death as a result of ALF. Furthermore, there is no evidence to show that the mechanism of liver injury is qualitatively different between patients with versus without encephalopathy. Indeed, hepatic encephalopathy is an important symptom used to predict whether a patient should undergo liver transplantation. Nevertheless, we believe it is important to prevent the progression to ALF before the development of encephalopathy to improve the prognosis of these patients. In other words, the present definition of ALF encourages us to delay liver-supporting treatments until encephalopathy becomes overt. Thus, we believe that the definition of ALF should be reviewed and reconstructed on the basis of current evidence.

Importantly, the theory that over-activation of macrophages is involved in the progression of ALF might be common to most patients with ALF, regardless of the trigger. Therefore, it is reasonable to classify patients with acute liver injury, with or without encephalopathy, according to the grade of intrahepatic macrophage activation. If TASIT suppresses macrophage activation, such a classification would be clinically relevant as an indication for TASIT, replacing the traditional definition of ALF based on the existence of encephalopathy.

The next question to answer is how we can determine the grade/contribution of intrahepatic macrophage activation. Based on our clinical experience with TASIT, we have uncovered the following important findings: (1) Patients with high serum ferritin concentrations showed strong coagulopathy, regardless of the triggers; (2) The serum levels of LDH are correlated with those of ferritin; (3) In some patients, serum LDH and/or serum ferritin concentrations remained around the normal limit while serum ALT exceeded 1 000 U/L; (4) Among the patients with high levels of serum LDH and ALT activity, some showed an abrupt spontaneous decrease in LDH after observation for 6 to 12 h while ALT levels remained elevated; (5) TASIT was mainly effective in patients with a high serum ferritin concentration which was not influenced by the etiology of liver injury; (6) For patients with effective TASIT, the serum LDH concentration decreased abruptly compared with the changes in ALT levels; and (7) Some patients without excessively high ferritin or LDH progressed to liver failure when their ALT levels remained elevated for a long period.

Based on these findings, we have proposed a mechanism underlying the progression of acute liver injury with coagulopathy/ALF (Figure 1). Acute hepatitis is caused by various triggers such as viruses, chemicals and autoimmune disorders. Most viruses and autoimmune disorders damage hepatocytes *via* cytotoxic T cells while hepatotoxic chemicals do so directly. We call these processes the "first hit". Although the first hit is usually not sufficient to lead to ALF, a vigorous and/or prolonged first hit could result in ALF. In some patients experiencing the first hit, over-activation of macrophages occurs in the liver, leading to disturbed intrahepatic microcirculation and massive hepatocytic death. The grade of macrophage activation and the consequent microcirculatory disturbances can be estimated by the serum ferritin and LDH levels respectively[32]. We call the process involved in macrophage activation the "second hit". The activation of macrophages spontaneously declines in some patients who may recover naturally. However, if macrophage activation is prolonged, the risk of death due to liver failure is greatly increased. The intensity and range of liver damage, represented by prolonged PT and elevated serum ALT concentrations, are determined by the sum of the first and second hits. TASIT is thought to be effective by preventing the second hit. Therefore, TASIT should be effective in patients whose liver failure is mainly caused by the second hit but not for those with first-hit-dominant liver failure.

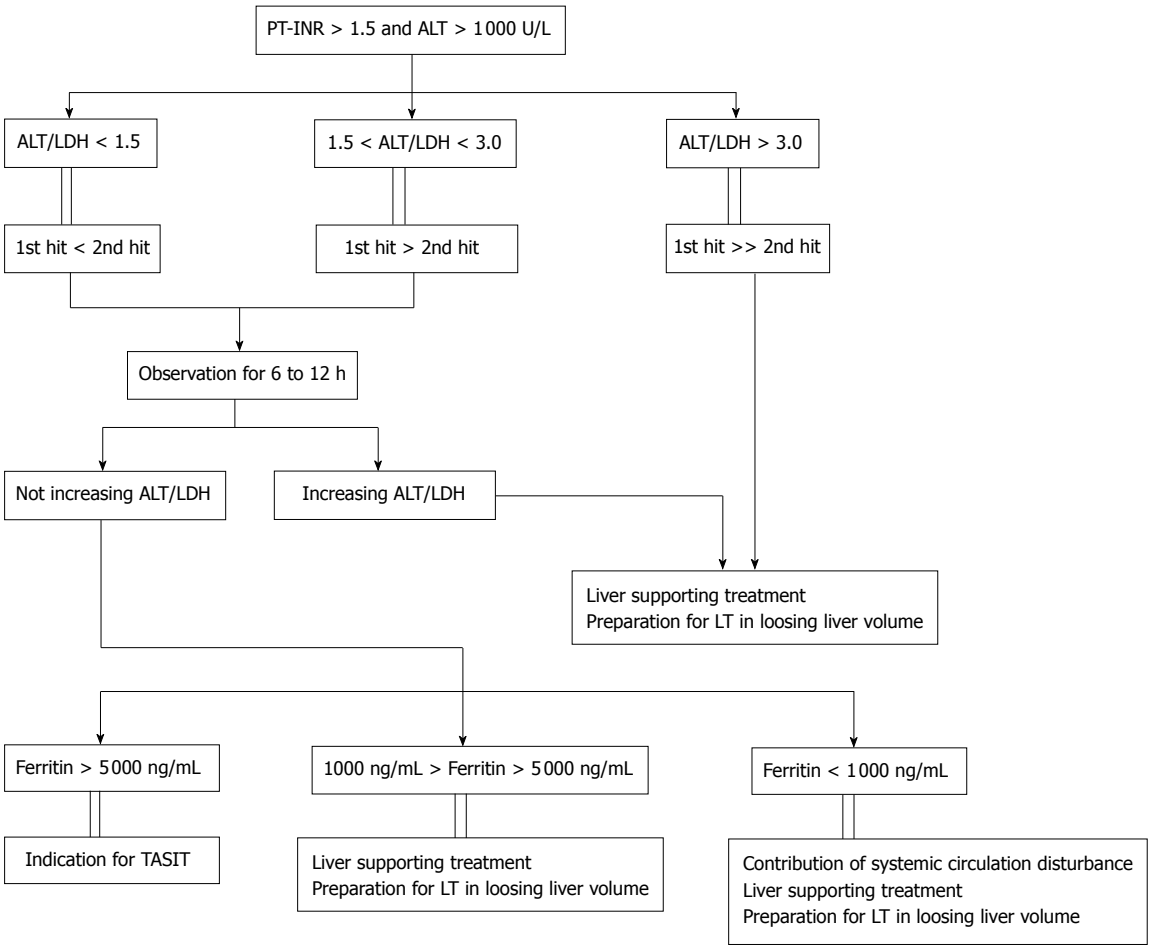


Figure 2 A method to classify patients with acute liver failure (acute liver injury) based on the grade of intrahepatic macrophage activation. First, patients are classified by their alanine aminotransferase (ALT)/lactate dehydrogenase (LDH) ratio which indicates the degree of hypoxia in liver. When a patient has a high serum concentration of LDH compared with that of ALT, the extent of the involvement of macrophage activation is estimated by the serum ferritin concentration. TASIT: transcatheter arterial steroid injection therapy. PT: prothrombin time; LT: liver transplantation.

CLASSIFICATION OF ACUTE LIVER INJURY WITH COAGULOPATHY

Patients admitted to our hospital with acute liver injury (ALT > 1 000 U/L) and coagulopathy (PT-INR > 1.5) show an elevated ALT/LDH ratio (Figure 2). Based on our experience, ratios < 1.5 represent liver injury mainly caused by the second hit while ratios of 1.5-3.0 indicate equal contributions of the first and second hit. Meanwhile, for patients with an ALT/LDH ratio > 3.0, the liver injury is due to a first-hit-dominant mechanism. In the third condition, we can provide liver-supporting treatment to prevent first hit and continue until liver transplantation can be performed.

For patients with an ALT/LDH ratio < 3.0, we monitor the ratio for 6-12 h. In some patients, the ratio increases abruptly during this period because of a decrease in the LDH concentration. This phenomenon likely reflects spontaneous improvement of the intrahepatic microcirculatory disturbances. In these patients, the serum ferritin levels are generally high although they decrease soon thereafter. Most patients with a rapid increase in the ALT/LDH ratio show improvements in coagulopathy but some still progress liver failure because the liver is thought to be severely damaged by the first hit. Most patients without an increase in the ALT/LDH ratio during the observation period present with remarkably elevated serum ferritin levels (> 5 000 ng/mL) and we perform TASIT in these patients. However some patients have relatively low serum ferritin levels (1 000-5 000 ng/mL) and the liver damage in these patients may be due to a first-hit-dominant mechanism. Therefore, we proceed with liver-supporting treatments and liver transplantation. In a few patients, the serum ferritin level is < 1 000 ng/mL but they have a low ALT/LDH ratio. We believe that systemic circulatory disorders may be present in these exceptional cases.

Our system is useful not only to determine the indication of TASIT or to prepare patients for liver transplantation in the early stage of the disease, but is also helpful to diagnose patients with rare etiologies. For example, we experienced a 40 year old man with an extremely high level of serum ferritin (55 775 ng/mL) despite a relatively high ALT/LDH ratio (2.6). The high ferritin level would normally suggest second-hit-dominant liver injury but this was not supported by the ALT/LDH ratio which should have been lower if ferritin was derived from the liver. We

considered that most of serum ferritin was derived from extra-hepatic organs and we subsequently found that he was suffering from chronic active EB virus infection. Similarly, we diagnosed a 35 year old woman with acute-onset of Budd-Chiari syndrome after finding a low ALT/LDH ratio and a normal serum ferritin concentration in this patient. Both cases were diagnosed quickly after admission because of our system to manage acute liver injury and the use of a classification method based on the intrahepatic macrophage activation theory.

PROBLEMS TO BE CLARIFIED

We believe that our classification system is useful to better understand the processes underlying liver injury; however, there are several problems to be clarified. Firstly, we do not know what causes over-activation of intrahepatic macrophages. Most patients with acute hepatitis are cured without developing coagulopathy and over-activation of macrophages seldom occurs in these patients. Even in patients with macrophage over-activation, this activation spontaneously regresses in some patients. What determines the duration of macrophage over-activation? Both the host's condition and the etiologies such as viruses and drugs may be responsible for the behavior of the macrophages. Secondly, it is unclear how activated macrophages cause microcirculatory disturbances. Although we believe that cytokines released from activated macrophages harm endothelial cells, no evidence for this has been reported to date. If we can clarify the underlying processes, we could develop more effective procedures than TASIT to suppress macrophage activation.

Although TASIT is certainly effective for patients with second-hit-dominant liver injury, the procedure has to be performed in the early stage of the disease, ideally during the period corresponding to the peak serum ALT level. Once the liver becomes obviously atrophic, it is difficult to rescue the patients, even with TASIT, most likely because a large amount of fibrin has accumulated in the sinusoids in the late stage of the disease. Clearly, a new approach other than TASIT is needed to overcome this problem. Indeed, for patients in whom liver failure proceeds in the absence of intrahepatic macrophage activation, there is still no effective method to prevent the disease progression. In our experience, TASIT was ineffective for patients with first-hit-dominant liver injury and liver transplantation was ultimately needed for these patients.

In our hospital, the overall prognosis of patients with acute liver injury and coagulopathy has improved because of our classification system and the introduction of TASIT. In Japan, ALF is caused by hepatitis viruses in more than half of the patients whereas acetaminophen is the major cause of ALF in European countries[33]. It is possible that TASIT is not effective for acetaminophen-induced liver injury because it may be a first-hit-dominant type. Therefore, further treatments are needed for such patients.

CONCLUSION

Recent discussions of ALF have mainly focused on the ability to predict prognosis because appropriate guidelines are needed to identify patients who will die without liver transplantation[34-37]. Accordingly, this trend is based on the notion that liver transplantation is the only effective method to rescue patients with ALF. Considering the limited supply of donors, liver transplantation cannot improve the prognosis of all patients with ALF. To reduce the number of patients who die from ALF, we must halt disease progression before ALF proceeds to the end-stage and we must develop new methods to treat patients and systems to classify patients to select the most appropriate treatment. Here, we have proposed such systems in response to these demands. We hope that further studies can elucidate the underlying mechanism involved in the development and progression of ALF and allow us to develop more effective systems and treatment for patients with acute liver injury.

REFERENCES

1 **Lee WM**, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. *Hepatology* 2008; **47**: 1401-1415
2 **Stravitz RT**, Kramer DJ. Management of acute liver failure. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 542-553
3 **Grodzicki M**, Kotulski M, Leonowicz D, Zieniewicz K, Krawczyk M. Results of treatment of acute liver failure patients with use of the prometheus FPSA system. *Transplant Proc* 2009; **41**: 3079-3081
4 **Marudanayagam R**, Shanmugam V, Gunson B, Mirza DF, Mayer D, Buckels J, Bramhall SR. Aetiology and outcome of acute liver failure. *HPB (Oxford)* 2009; **11**: 429-434
5 **Hiramatsu A**, Takahashi S, Aikata H, Azakami T, Katamura Y, Kawaoka T, Uka K, Yamashina K, Takaki S, Kodama H, Jeong SC, Imamura M, Kawakami Y, Chayama K. Etiology and outcome of acute liver failure: retrospective analysis of 50 patients treated at a single center. *J Gastroenterol Hepatol* 2008; **23**: 1216-1222
6 **Canbay A**, Jochum C, Bechmann LP, Festag S, Gieseler RK, Yüksel Z, Lütkes P, Saner FH, Paul A, Gerken G. Acute liver failure in a metropolitan area in Germany: a retrospective study (2002 - 2008). *Z Gastroenterol* 2009; **47**: 807-813
7 **Akdogan M**, Camci C, Gurakar A, Gilcher R, Alamian S, Wright H, Nour B, Sebastian A. The effect of total plasma exchange on fulminant hepatic failure. *J Clin Apher* 2006; **21**: 96-99
8 **Davenport A**, Will EJ, Davison AM. Effect of renal replacement therapy on patients with combined acute renal and fulminant hepatic failure. *Kidney Int Suppl* 1993; **41**: S245-S251
9 **Sato S**, Suzuki K, Takikawa Y, Endo R, Omata M. Clinical epidemiology of fulminant hepatitis in Japan before the substantial introduction of liver transplantation: an analysis of 1309 cases in a 15-year national survey. *Hepatol Res* 2004; **30**: 155-161
10 **Sekido H**, Matsuo K, Takeda K, Ueda M, Morioka D, Kubota T, Tanaka K, Endo I, Togo S, Shimada H. Usefulness of artificial liver support for pretransplant patients with fulminant hepatic failure. *Transplant Proc* 2004; **36**: 2355-2356
11 **Antoniades CG**, Berry PA, Wendon JA, Vergani D. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol* 2008; **49**: 845-861
12 **Chun LJ**, Tong MJ, Busuttil RW, Hiatt JR. Acetaminophen

hepatotoxicity and acute liver failure. *J Clin Gastroenterol* 2009; **43**: 342-349
13 **Fontana RJ**. Acute liver failure due to drugs. *Semin Liver Dis* 2008; **28**: 175-187
14 **Matsui A**, Mochida S, Ohno A, Nagoshi S, Hirose T, Fujiwara K. Plasma osteopontin levels in patients with fulminant hepatitis. *Hepatol Res* 2004; **29**: 202-206
15 **Hiraoka A**, Horiike N, Akbar SM, Michitaka K, Matsuyama T, Onji M. Soluble CD163 in patients with liver diseases: very high levels of soluble CD163 in patients with fulminant hepatic failure. *J Gastroenterol* 2005; **40**: 52-56
16 **Møller HJ**, Gronbaek H, Schiodt FV, Holland-Fischer P, Schilsky M, Munoz S, Hassanein T, Lee WM. Soluble CD163 from activated macrophages predicts mortality in acute liver failure. *J Hepatol* 2007; **47**: 671-676
17 **Kotoh K**, Ueda A, Tanaka M, Miyazaki M, Kato M, Kohjima M, Enjoji M, Nakamuta M, Takayanagi R. A high prevalence of extreme hyperferritinemia in acute hepatitis patients. Hepatic Medicine: Evidence and Research 2009; **1**: 1-7
18 **Janka GE**. Hemophagocytic syndromes. *Blood Rev* 2007; **21**: 245-253
19 **Ravelli A**. Macrophage activation syndrome. *Curr Opin Rheumatol* 2002; **14**: 548-552
20 **Allen CE**, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2008; **50**: 1227-1235
21 **Prieto J**, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver diseases. *Gastroenterology* 1975; **68**: 525-533
22 **Eastham EJ**, Bell JI, Douglas AP. Serum ferritin levels in acute hepatocellular damage from paracetamol overdosage. *Br Med J* 1976; **1**: 750-751
23 **Hengeveld P**, Zuyderhoudt FM. Iron mobilisation with chelating agents during acute viral hepatitis. *Hepatogastroenterology* 1982; **29**: 191-194
24 **Hengeveld P**, Zuyderhoudt FM, Jöbsis AC, van Gool J. Some aspects of iron metabolism during acute viral hepatitis. *Hepatogastroenterology* 1982; **29**: 138-141
25 **Milman N**, Graudal N. Serum ferritin in acute viral hepatitis. *Scand J Gastroenterol* **1984**; 19: 38-40
26 **Triadou P**, Regnat-Lusinchi A, Girot R. Use of the ferritin/alanine aspartate transaminase ratio as an iron overload marker independent of liver cell damage. *Eur J Haematol* 1989; **43**: 423-427
27 **Rees BB**, Bowman JA, Schulte PM. Structure and sequence conservation of a putative hypoxia response element in the lactate dehydrogenase-B gene of Fundulus. *Biol Bull* 2001; **200**: 247-251
28 **Koukourakis MI**, Giatromanolaki A, Sivridis E, Gatter KC, Harris AL. Lactate dehydrogenase 5 expression in operable colorectal cancer: strong association with survival and activated vascular endothelial growth factor pathway--a report of the Tumour Angiogenesis Research Group. *J Clin Oncol* 2006; **24**: 4301-4308
29 **Firth JD**, Ebert BL, Pugh CW, Ratcliffe PJ. Oxygen-regulated control elements in the phosphoglycerate kinase 1 and lactate dehydrogenase A genes: similarities with the erythropoietin 3' enhancer. *Proc Natl Acad Sci USA* 1994; **91**: 6496-6500
30 **Arai M**, Mochida S, Ohno A, Ogata I, Fujiwara K. Sinusoidal endothelial cell damage by activated macrophages in rat liver necrosis. *Gastroenterology* 1993; **104**: 1466-1471
31 **Kotoh K**, Enjoji M, Nakamuta M, Yoshimoto T, Kohjima M, Morizono S, Yamashita S, Horikawa Y, Yoshimitsu K, Tajima T, Asayama Y, Ishigami K, Hirakawa M. Arterial steroid injection therapy can inhibit the progression of severe acute hepatic failure toward fulminant liver failure. *World J Gastroenterol* 2006; **12**: 6678-6682
32 **Kotoh K**, Enjoji M, Kato M, Kohjima M, Nakamuta M, Takayanagi R. A new parameter using serum lactate dehydrogenase and alanine aminotransferase level is useful for predicting the prognosis of patients at an early stage of acute liver injury: a retrospective study. *Comp Hepatol* 2008; **7**: 6
33 **Gregory B**, Larson AM, Reisch J, Lee WM. Acetaminophen dose does not predict outcome in acetaminophen-induced acute liver failure. *J Investig Med* 2010; **58**: 707-710
34 **Peláez-Luna M**, Martinez-Salgado J, Olivera-Martinez MA. Utility of the MAYO End-Stage Liver Disease score, King's College Criteria, and a new in-hospital mortality score in the prognosis of in-hospital mortality in acute liver failure. *Transplant Proc* 2006; **38**: 927-929
35 **Schiødt FV**, Chung RT, Schilsky ML, Hay JE, Christensen E, Lee WM. Outcome of acute liver failure in the elderly. *Liver Transpl* 2009; **15**: 1481-1487
36 **Perkins JD**. Another formula to determine the prognosis of patients with acute liver failure. *Liver Transpl* 2009; **15**: 986-991
37 **McKenzie TJ**, Lillegard JB, Nyberg SL. Artificial and bioartificial liver support. *Semin Liver Dis* 2008; **28**: 210-217

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i11.401

World J Hepatol 2010 November 27; 2(11): 401-405
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

BRIEF ARTICLE

Clinical characteristics of null responders to Peg-IFNα2b/ribavirin therapy for chronic hepatitis C

Hideyuki Suzuki, Satoru Kakizaki, Norio Horiguchi, Takeshi Ichikawa, Ken Sato, Hitoshi Takagi, Masatomo Mori

Hideyuki Suzuki, Satoru Kakizaki, Norio Horiguchi, Takeshi Ichikawa, Ken Sato, Hitoshi Takagi, Masatomo Mori, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan

Author contributions: Suzuki H and Kakizaki S, designed the study, analyzed and interpreted data, and drafted the manuscript; Horiguchi N, Ichikawa T, Sato K, and Takagi H, treated the patients and provided clinical data and performed the liver biopsy; and Mori M, supervised the work.

Correspondence to: Satoru Kakizaki, MD, PhD, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. kakizaki@showa.gunma-u.ac.jp
Telephone: +81-27-2208127 Fax: +81-27-2208136
Received: August 12, 2010 Revised: November 4, 2010
Accepted: November 11, 2010
Published online: November 27, 2010

Abstract

AIM: To predict which chronic hepatitis C patients are likely to be late-responders, we herein investigated the clinical characteristics of null-responders at 36 wk with hepatitis C virus (HCV) genotype Ib and a high viral load during the course of pegylated interferon (Peg-IFN)/ribavirin therapy.

METHODS: One hundred forty-two patients with genotype Ib HCV and a high viral load were included in this study. Peg-IFNα2b (1.5 μg/kg once a week) and ribavirin (600-1000 mg per day according to body weight) were administered for 48 wk. We defined null-responders as the cases that never cleared serum HCV RNA as determined using RT-PCR until 36 wk. Other patients were defined as responders. We compared the clinical characteristics (age, gender, body mass index, previous treatment) and HCV RNA titer during the therapy between null-responders and responders.

RESULTS: The HCV RNA clearance rate was 17.9% (24/134), 46.3% (62/134), 60.6% (86/142), 86.6% (123/142), and 88.0% (125/142) at 4, 8, 12, 24, and 36 wk, respectively. There were 17 patients (12.0%) who were still null-responders at 36 wk. There were no differences in the clinical characteristics between the responders and null-responders except for the titer and decline rates of HCV RNA at 1 wk and 4 wk. The HCV RNA titers at 1 wk and after 4 wk of treatment were significantly higher in the null-responders in comparison to the responders (P <0.01). The serum HCV RNA titers of the responders decreased by 1.3 log after 1 wk of treatment, and 1.6 log after 4 wk of treatment, respectively. On the other hand, the titers of the null responders decreased by only 0.5 log after 1 wk, and 0.7 log after 4 wk of treatment, respectively. The decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders (P <0.01).

CONCLUSION: The HCV RNA titer at 1 wk and 4 wk after initiating treatment may be useful for predicting null-responders to Peg-IFNα2b/ribavirin therapy. However, further investigation is needed to determine the optimal time at which the decision to discontinue the Peg-IFNα2b/ribavirin therapy for null-responders can be made.

© 2010 Baishideng. All rights reserved.

Key words: Null responder; Pegylated interferon α2b; Ribavirin; Chronic hepatitis C

Peer reviewers: Qiang Liu, PhD, Vaccine and Infectious Disease Organization, University of Saskatchewan, 120 Veterinary Road, Saskatoon, Saskatchewan, S7N 5E3, Canada; Emmanouil Sinakos, MD, Aristotle University of Thessaloniki, 11A, Perdika Str., Pilea 55535, Greece; Toru Ishikawa, MD, Department of Gastroenterology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata 950-1104, Japan

Suzuki H, Kakizaki S, Horiguchi N, Ichikawa T, Sato K, Takagi H, Mori M. Clinical characteristics of null responders to Peg-IFNα2b/ribavirin therapy for chronic hepatitis C. *World J Hepatol* 2010; 2(11): 401-405 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i11/401.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i11.401

INTRODUCTION

Chronic hepatitis C is a major cause of liver cirrhosis and hepatocellular carcinoma[1,2]. Improvements in antiviral therapy for patients with hepatitis C virus (HCV) infection have recently been achieved by means of the use of pegylated interferon (Peg-IFN) combined with ribavirin[3-5], and this treatment strategy has become a standard therapy for the eradication of HCV infection. However, the sustained virological response (SVR) rates in patients with HCV genotype 1 and a high viral load are still insufficient, and the search continues for better treatment strategies. The treatment of patients with HCV genotype 1 with Peg-IFN and ribavirin for more than 48 wk has led to higher SVR rates. Although many studies have extended the duration of therapy from 48 wk to 72 wk, the optimal duration has not yet been determined. In the 2008 Japanese guidelines for the treatment of patients with chronic hepatitis C[6], treatment with Peg-IFN combined with ribavirin for 48 wk is indicated for treatment-naïve patients infected with genotype 1 HCV. Treatment is recommended to be continued for an addi tional 24 wk (72 wk total) in the patients who remained positive for HCV RNA (detectable by the real-time poly merase chain reaction) at 12 wk after the start of treatment, but who become negative for HCV RNA after 13-36 wk of treatment[6]. As a result, the prolonged treatment of the patients who still have evidence of HCV infection at 36 wk is not indicated when the normalization of the alanine aminotransferase (ALT) level is not achieved. Because Peg-IFN/ribavirin has many adverse effects, the patients who are null responders should cease the treatment and wait until commencing a new treatment regimen which includes protease inhibitors. It would therefore be useful to predict null responders earlier in the course of the treatment in order to both avoid adverse effects, and to achieve better disease control. We herein describe our investigation of the clinical characteristics of null-responders to Peg-IFN with ribavirin therapy with HCV genotype Ib and a high viral load.

MATERIALS AND METHODS

Patients

One hundred forty-two patients with chronic hepatitis C were included in this study. All patients fulfilled the following inclusion criteria: (1) HCV genotype Ib; (2) more than 10^5 copies/mL of HCV in the serum; and (3) an elevated serum ALT level for least 6 mo before initiation of treatment. In addition to these criteria, patients were excluded when they suffered from any of the following conditions: (1) decompensated liver disease; (2) other causes of liver disease such as hepatitis B infection; (3) autoimmune disorders; (4) hemoglobin value < 11 g/dL; (5) white blood cell count < 3 000/μL; (6) thrombocytopenia < 70 000/μL; (7) neoplastic disease; (8) severe cardiac disease; (9) other severe concurrent diseases such as pre-existing psychiatric conditions; or (10) pregnancy or lactation. Informed consent was obtained from all patients enrolled in the study, after a thorough explanation of the aims, risks and benefits of this therapy.

Study design

One hundred forty-two patients received Peg-IFNα2b/ribavirin therapy from December 2005 to July 2006 at Gunma University Hospital and its affiliated hospitals. Patients received Peg-IFNα2b (1.5 μg/kg once a week; Schering-Plough, Tokyo), and 600 mg, 800 mg or 100 mg ribavirin per day orally, adjusted according to body weight (600 mg for weight under 60 kg, 800 mg for weight between 60 kg and 80 kg, 1000 mg for weight over 80 kg) for 48 wk. The patients were followed-up for another 24 wk after the treatment, i.e. until week 72. Clinical characteristics including age, gender, body mass index, and previous treatment, were analyzed. Serum biochemistry and the HCV RNA titer were measured at pre-treatment and after 4, 8, 12, 24, 36, 48, and 72 wk of treatment. We defined as "null-responders" the cases that did not clear serum HCV RNA (assessed using RT-PCR) by 36 wk. Other patients were defined as "responders". A sustained virological response (SVR) was defined as undetectable HCV RNA in serum after 24 wk of treatment. All the other patients whose HCV RNA was positive at 24 wk after the end of treatment were classified as non-SVR.

Histopathological examination of the liver

A liver biopsy was performed for patients who agreed, after an explanation of the aim and risks before treatment. Hepatic inflammation (grade) and fibrosis (stage) were assessed by the semiquantitative histological score proposed by Scheuer[7] and Desmet *et al*[8]. The amount of portal/periportal inflammatory activity, lobular inflammatory activity, and degenerative liver cell changes were scored, using a scale of 0 to 3 for the criterion 'inflammatory activity' (0: absent; 1: mild; 2: moderate; 3: severe). The degree of fibrosis was scored using a scale of 0 to 4 (0: absent; 1: mild without septa; 2: moderate with few septa; 3: numerous septa without cirrhosis; 4: cirrhosis).

Statistical analysis

Fisher's exact probability test for frequency tables was used for statistical analysis. Distributions of continuous variables were analyzed by the Mann-Whitney *U*-test. P value < 0.05 was considered significant.

RESULTS

Clinical characteristics and response to therapy

Patients' characteristics are shown in Table 1. The male:

Table 1 The characteristics of patients with chronic hepatitis C treated by pegylated interferon/ribavirin therapy

Characteristics		
Number of patients	*n*	142
Gender	Male; Female	80; 62
Mean age (range)	Years	56.0 ± 10.0 (19-71)
Body weight	kg	63.3 ± 10.9 (40-98)
Body mass index	kg/m^2	25.3 ± 3.0
ALT	U/L	85.3 ± 64.5
HCV RNA titer	KIU/mL	1927 ± 1415
Previous treatment	Naïve/Retreatment	97/45
Histology		
Fibrosis	F0/F1/F2/F3/F4	4/30/28/21/5
Activity	A0/A1/A2/A3	0/32/54/2

ALT: alanine aminotransferase; HCV: hepatitis C virus.

female ratio was 80:62. The mean patient age was 56.0 ± 10.0 years old (range 19-71). Mean body mass index was 25.3 ± 3.0 kg/m^2. Ninety-seven patients were naïve for IFN treatment, and 45 patients had received previous treatment. Eighty-eight patients underwent a liver biopsy. Inflammatory activity was classified as A0: 0; A1:32; A2: 54; and A3: 2 patients, and the fibrosis score was F0: 4; F1: 30; F2: 28;, F3: 21; and F4: 5 patients, respectively. At the end of the study (72 wk), the overall SVR rate of all patients was 60/142 (42.3%), that of responders was 60/125 (48.0%) and that of null responders was 0/17 (0.0%).

Factors associated with a null response

There were 17 patients (12.0%) who were null-responders at 36 wk. A comparison of the clinical characteristics between the responders and null responders is shown in Table 2. There were no significant differences between responders and null responders with regard to gender, age, body weight, body mass index, previous treatment with IFN, baseline HCV RNA levels, serum ALT levels, or stage of fibrosis (Table 2). However, the HCV RNA levels at 1 wk and 4 wk after initiating treatment were significantly higher in null responders ($P < 0.01$). The null responders to Peg-IFNα2b/ribavirin had little or no decrease in the serum HCV RNA after 4 wk in therapy. The serum HCV RNA titers of the responders decreased by 1.3 log after 1 wk of treatment and 1.6 log after 4 wk of treatment, respectively. On the other hand, the titers of the null responders decreased by only 0.5 log after 1 wk and 0.7 log after 4 wk of treatment, respectively. The decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders ($P < 0.01$).

DISCUSSION

The guidelines in Japan for the treatment of patients with chronic hepatitis C recommend that Peg-IFN/ribavirin treatment is continued for 72 wk in patients who have remained positive for HCV RNA after 12 wk of treatment, but who become negative for HCV RNA after 13-36 wk

Table 2 Comparison of the clinical characteristics between responders and null responders

		Responders	Null responders	*P*
Number of patients	*n*	123	17	NS
Gender	Male; Female	70; 53	10; 7	NS
Mean age (range)	Years	56.3 ± 10.2	57.2 ± 7.5	NS
Body weight	kg	62.6 ± 11.0	62.3 ± 12.0	NS
Body mass index	kg/m^2	23.4 ± 3.1	24.2 ± 2.9	NS
Previous treatment	Naïve/ Retreatment	84/41	13/4	NS
ALT	U/L	88.5 ± 66.2	68.4 ± 45.0	NS
HCV RNA titer				
Pre-treatment	KIU/mL	1849 ± 1362	2217 ± 1584	NS
1 wk	KIU/mL	267 ± 338	1173 ± 838	$P < 0.01$
4 wk	KIU/mL	50 ± 104	472 ± 427	$P < 0.01$
Fibrosis	F0-1/F2-4	27/44	7/10	NS

ALT: alanine aminotransferase; HCV: hepatitis C virus.

on treatment[6]. Based on these guidelines, the patients who are positive for HCV infection after 36 wk of treatment are not recommended for prolonged therapy, and should cease the treatment when the normalization of the ALT level is not achieved. We conducted this study to determine whether it is possible to predict which patients will be non-responsive to the treatment.

There were no significant differences in the clinical characteristics between the responders and null-responders, except for the titer and decline rates of HCV RNA at 1 wk and 4 wk respectively after starting treatment. HCV RNA titers after 1 wk and 4 wk of treatment were significantly higher in null-responders compared with responders. Furthermore, the decrease rates of HCV RNA after 1 and 4 wk of treatment were significantly worse for null responders than for the responders. These results seem to be reasonable, because null responders had little or no decrease in their HCV RNA titer. The probability of SVR is also dependent on the speed of the decline in the viral load[9]. A faster HCV RNA decline to an undetectable level means longer duration viral suppression, which can be translated to a higher chance of SVR. A large combined dataset including 569 genotype I HCV infected patients treated by Peg-IFN/ribavirin for 48 wk showed that 88% of the patients who achieved rapid viral response (RVR), undetectable HCV RNA after 4 wk of therapy, achieved SVR, in comparison to 68% of patients with complete EVR (complete early viral response, undetectable HCV RNA from baseline after 12 wk of therapy) and 29% of patients with partial EVR (partial EVR, decline of > 2 $\log_{10}$ IU/mL from baseline after 12 wk of therapy)[10]. Although the HCV RNA titer during treatment may be a useful predictive factor for null-responders in Peg-IFNα2b/ribavirin therapy, further studies are needed to confirm our findings and to identify other useful predictive factors.

In the present study, the null response was not associated with gender, age, or previous IFN therapy. With

regard to gender, it has been reported that male patients have a higher tendency to achieve SVR than female patients[11]. However, this was not shown to be the case in our study of null-responders. Regarding age, there have been reports suggesting that there is a relationship between patient age and SVR[12,13]. Although the SVR rate is reported to be lower in elderly patients than in younger patients[12], there were no differences in age between null-responders and responders in this study. In our study, previous IFN therapy did not affect the null-response. The reasons for the equivalent response rates in subjects with a prior IFN history are unclear. Further validation using larger-scale studies is required to clarify the significance of these factors in null responders.

There are many predictive factors for SVR in Peg-IFN/ribavirin therapy. The virus itself is one factor, and it has been reported that amino acid substitutions in the core region are regarded as predictors of the response to Peg-IFN/ribavirin therapy in Japanese patients infected with HCV genotype Ib[14-16]. The substitution of amino acid (aa) 70 and 91 in the core region can predict the response to Peg-IFN/ribavirin combination therapy[14-16]. Mutations in the interferon sensitivity determining region (ISDR) are also associated with the response to combi nation therapy with Peg-IFN/ribavirin[17-20]. It has been reported that amino acid substitutions in the core and mutations in the ISDR are predictive of virological response to combination therapy in patients with HCV geno type Ib and a high viral load[16]. On the other hand, single nucleotide polymorphisms (SNPs) near the *IL28B* gene on chromosome 19 in the host have been suggested to be strongly associated with a null virological response[21-23]. Host genetics also may be useful for predicting the drug response.

In conclusion, the HCV RNA titer after 1 wk and 4 wk of treatment may be a useful predictive factor for null-responders to Peg-IFNα2b/ribavirin therapy. However, further investigation is needed to determine the optimal time when Peg-IFNα2b/ribavirin therapy should be discontinued for null-responders.

COMMENTS

Background

The 2008 Japanese guidelines for the treatment of patients with chronic hepatitis C state that with pegylated interferon (Peg-IFN) combined with ribavirin for 48 wk is indicated for the patients with genotype 1 and a high viral load. Treatment is recommended to be continued for an additional 24 wk (72 wk total) in the patients who remain positive for hepatitis C virus (HCV) RNA at 12 wk after the start of treatment, but who become negative for HCV RNA after 13-36 wk of treatment. The prolonged treatment of the patients who still have evidence of HCV infection at 36 wk is therefore not indicated when the alanine aminotransferase (ALT) level is not normalized. Null responders should therefore cease this treatment and wait for the development of a novel treatment regimen, such as protease inhibitors, because Peg-IFN/ribavirin has many adverse effects.

Research frontiers

We investigated the clinical characteristics of null-responders at 36 wk with HCV genotype Ib and a high viral load during the course of Peg-IFN/ribavirin therapy to predict the patients who are likely to be late-responders.

Innovations and breakthroughs

The HCV RNA titer at 1 wk and 4 wk after initiating treatment may be useful for predicting null-responders to Peg-IFN/ribavirin therapy.

Applications

It would be useful to predict null responders earlier in the course of the disease in order to both avoid adverse effects and to achieve better disease control. However, further investigation is needed to determine the optimal time to determine whether to discontinue the Peg-IFN/ribavirin therapy for null-responders.

Peer reviews

Hepatitis C continues to be an important public health issue worldwide. How to deliver individualized therapy with interferon and ribavirin is a significant challenge. Therefore, the authors evaluated clinical and virological parameters before and after therapy in 142 patients with HCV genotype Ib. The conclusion was that higher HCV titers at week 1 and 4 after therapy can predict null response. This is an interesting report of clinical characteristics of null responders to Peg-IFN/RBV therapy for chronic hepatitis C. It is of clinical significance.

REFERENCES

1 **Di Bisceglie AM**. Hepatitis C. *Lancet* 1998; **351**: 351-355
2 **Marcellin P**. Hepatitis C: the clinical spectrum of the disease. *J Hepatol* 1999; **31** Suppl 1: 9-16
3 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965
4 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982
5 **Zeuzem S**, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O'Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; **343**: 1666-1672
6 **Kumada H**, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Chayama K, Sakisaka S, Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. *Hepatol Res* 2010; **40**: 8-13
7 **Scheuer PJ**. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991; **13**: 372-374
8 **Desmet VJ**, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; **19**: 1513-1520
9 **Teoh NC**, Farrell GC, Chan HL. Individualisation of antiviral therapy for chronic hepatitis C. *J Gastroenterol Hepatol* 2010; **25**: 1206-1216
10 **Fried MW**, Jensen DM, Rodriguez-Torres M, Nyberg LM, Di Bisceglie AM, Morgan TR, Pockros PJ, Lin A, Cupelli L, Duff F, Wang K, Nelson DR. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. *Hepatology* 2008; **48**: 1033-1043
11 **Sezaki H**, Suzuki F, Kawamura Y, Yatsuji H, Hosaka T, Akuta N, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Miyakawa Y, Kumada H. Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. *Dig Dis Sci* 2009; **54**: 1317-1324
12 **Honda T**, Katano Y, Shimizu J, Ishizu Y, Doizaki M, Hayashi K, Ishigami M, Itoh A, Hirooka Y, Nakano I, Urano F, Yoshioka K, Toyoda H, Kumada T, Goto H. Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. *Liver Int* 2010; **30**: 527-537
13 **Hung CH**, Chen CH, Lee CM, Wu CM, Hu TH, Wang JH, Yen YH, Lu SN. Association of amino acid variations in the NS5A and E2-PePHD region of hepatitis C virus 1b with hepatocellular carcinoma. *J Viral Hepat* 2008; **15**: 58-65
14 **Akuta N**, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzu-

ki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. Amino acid substitutions in the hepatitis C virus core region are the important predictor of hepatocarcinogenesis. *Hepatology* 2007; **46**: 1357-1364

15 **Akuta N**, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Watahiki S, Sato J, Kobayashi M, Arase Y, Ikeda K, Kumada H. Predictive factors of virological non-response to interferon-ribavirin combination therapy for patients infected with hepatitis C virus of genotype 1b and high viral load. *J Med Virol* 2006; **78**: 83-90

16 **Mori N**, Imamura M, Kawakami Y, Saneto H, Kawaoka T, Takaki S, Aikata H, Takahashi S, Chayama K. Randomized trial of high-dose interferon-alpha-2b combined with ribavirin in patients with chronic hepatitis C: Correlation between amino acid substitutions in the core/NS5A region and virological response to interferon therapy. *J Med Virol* 2009; **81**: 640-649

17 **Yen YH**, Hung CH, Hu TH, Chen CH, Wu CM, Wang JH, Lu SN, Lee CM. Mutations in the interferon sensitivity-determining region (nonstructural 5A amino acid 2209-2248) in patients with hepatitis C-1b infection and correlating response to combined therapy of pegylated interferon and ribavirin. *Aliment Pharmacol Ther* 2008; **27**: 72-79

18 **Hung CH**, Lee CM, Lu SN, Lee JF, Wang JH, Tung HD, Chen TM, Hu TH, Chen WJ, Changchien CS. Mutations in the NS5A and E2-PePHD region of hepatitis C virus type 1b and correlation with the response to combination therapy with interferon and ribavirin. *J Viral Hepat* 2003; **10**: 87-94

19 **Murayama M**, Katano Y, Nakano I, Ishigami M, Hayashi K, Honda T, Hirooka Y, Itoh A, Goto H. A mutation in the interferon sensitivity-determining region is associated with responsiveness to interferon-ribavirin combination therapy in chronic hepatitis patients infected with a Japan-specific subtype of hepatitis C virus genotype 1B. *J Med Virol* 2007; **79**: 35-40

20 **Shirakawa H**, Matsumoto A, Joshita S, Komatsu M, Tanaka N, Umemura T, Ichijo T, Yoshizawa K, Kiyosawa K, Tanaka E. Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients using viral and host factors. *Hepatology* 2008; **48**: 1753-1760

21 **Ge D**, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399-401

22 **Tanaka Y**, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105-1109

23 **Suppiah V**, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100-1104

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i11.406

World J Hepatol 2010 November 27; 2(11): 406-409
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

CASE REPORT

Hepatic portal venous gas due to cryptosporidiosis in a patient with acquired immunodeficiency syndrome

Nilesh Lodhia, Atif Ali, Joel Bessoff

Nilesh Lodhia, Atif Ali, Joel Bessoff, School of Medicine, University of Tennessee, Memphis, TN 38103, United States
Author contributions: Lodhia N, Ali A, and Bessoff J were involved in literature research, data analysis, and manuscript preparation.
Correspondence to: Joel Bessoff, MD, Department of Internal Medicine, Division of Gastroenterology, University of Tennessee, Memphis, TN 38103, United States. jbessoff@uthsc.edu
Telephone: +1-901-5456320
Received: June 29, 2010 Revised: November 8, 2010
Accepted: November 15, 2010
Published online: November 27, 2010

Abstract

Although the presence of hepatic portal venous gas (HPVG) on computed tomography (CT) is typically an ominous finding, HPVG may sometimes be less catastrophic. The clinical significance of HPVG is variable, and it depends primarily on the underlying pathology. We report a case of a patient with acquired immunodeficiency syndrome (AIDS) who was found to have HPVG on CT as a presumed result of gastrointestinal cryptosporidiosis, an association that, to our knowledge, has not been reported. This case illustrates another cause of HPVG that should be considered in patients with AIDS.

© 2010 Baishideng. All rights reserved.

Key words: Hepatic portal venous gas; Cryptosporidiosis; Acquired immunodeficiency syndrome

Peer reviewers: Radha Krishan Dhiman, MD, DM, FACG, Professor, Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India; Joel Faintuch, MD, PhD, Department of Gastroenterology, Hospital das Clinicas, ICHC, 9th Floor, Room 9077, Sao Paulo 05403-900, Brazil

Lodhia N, Ali A, Bessoff J. Hepatic portal venous gas due to cryptosporidiosis in a patient with acquired immunodeficiency syndrome. *World J Hepatol* 2010; 2(11): 406-409 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i11/406.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i11.406

INTRODUCTION

The presence of hepatic portal venous gas (HPVG) on computed tomography (CT) is typically an ominous finding that is associated with significant morbidity and mortality. It is most commonly associated with bowel necrosis (72%), followed by ulcerative colitis (8%), intra-abdominal abscesses (6%), small bowel obstruction (3%) and gastric ulcers (3%)[1]. The frequent association with bowel necrosis can explain the 56%-90% mortality rate associated with HPVG[2].

We report a case of a patient with acquired immunodeficiency syndrome (AIDS) who was found to have HPVG on CT as a presumed result of gastrointestinal Cryptosporidiosis. This association, to our knowledge, has never been reported.

CASE REPORT

A 47-year-old African American female with a history of AIDS with a CD4 count of 12 (confirmed by repeated measurements) presented with diarrhea, dizziness, and fatigue over a period of three weeks. Her vitals on admission were as follows: temperature 37.3℃, heart rate 103/min, blood pressure 93/65 mmHg, and respiratory rate of 20/min. On physical exam she had diffuse mild abdominal pain, tachycardia, and poor skin turgor. Initial laboratory results: white blood cell (WBC) 6.4 k/μL, hemoglobin (Hb) 8.3 g/dL, platelets (PLT) 252 000/cc^3, sodium 141 mmol/L, potassium 3.6 mmol/L, chloride 111 mmol/L, bicarbonate 22 mmol/L, BUN 14 mg/dL,

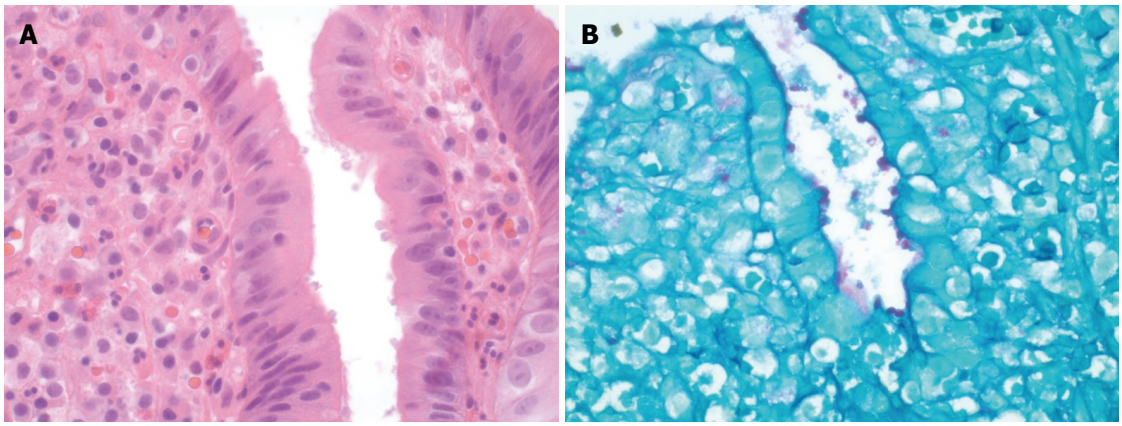


Figure 1 Cryptosporidium microorganisms shown by the biopsy. A: On the surface epithelium of the terminal ileum; B: On the surface epithelium of the duodenum (Periodic acid schiff stain).

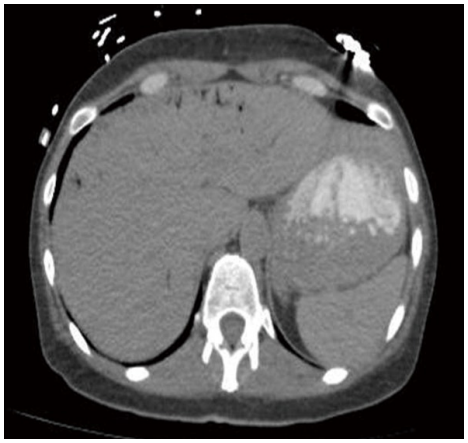


Figure 2 Non-contrast axial computed tomography of the upper abdomen demonstrates multiple peripheral linear branching air density str uctures consistent with portal venous air.

creatinine 3.8 mg/dL, and glucose 100 mg/dL. Her baseline creatinine was less than 1.0 mg/dL. Stool studies for *Clostridium Difficile*, acid-fast bacilli, fecal leukocytes, culture, and ova and parasites were all negative. A non-contrast computed tomography (CT) of the abdomen and pelvis did not show any acute findings. Colonoscopy was normal from the ileum to the rectum. Random biopsies were taken from the terminal ileum, colon, and rectum. The biopsy from the terminal ileum was identified as having numerous parasitic organisms morphologically consistent with *Cryptosporidium Parvum* (Figure 1A). The patient was discharged on a 7 d course of metronidazole with plans to start highly active antiretroviral therapy (HAART) as an outpatient.

Prior to initiating HAART therapy, the patient returned one week later with profuse bloody diarrhea, abdominal pain, and oliguria. She was alert and oriented, but appeared weak. She had a temperature of 37.0℃, heart rate of 101/min, blood pressure 88/61 mmHg, and a respiratory rate of 18/min. Her abdomen was soft and non-tender with positive bowel sounds. Laboratory results: WBC 10.9 k/μL, Hb 11.6 gm/dL, PLT 250 000/cc^3, sodium 135 mmol/dL, potassium 4.2 mmol/dL, chloride 109 mmol/dL, bicarbonate 9 mmol/dL, BUN 34 mg/dL, creatinine 13 mg/dL, and glucose 159 mg/dL. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase were normal. The albumin was 2.1 g/dL, with an international normalized ratio (INR) of 1.24. She was admitted to the medical intensive care unit (MICU) for further management. Eso phagastroduodenoscopy (EGD) showed normal findings from the proximal esophagus to the antrum. The duodenum had a 3-mm submucosal nodule in the duodenal bulb and a 5-mm submucosal nodule in the duodenal apex. Biopsy of the duodenal nodules showed ulcerated, active chronic duodenitis with numerous organisms morphologically consistent with *Cryptosporidium Parvum* present in the epithelial surface; Periodic acid schiff (PAS) stain was positive (Figure 1B).

Several days into her admission, she continued to have hypotension, tachycardia, and vague abdominal pain. A non-contrast abdominal CT was repeated, which showed diffuse portal venous gas. In addition, there were small bubbles of gas distributed in a linear fashion in the anterior abdomen, along the transverse colon, likely within venous branches, although no definite evidence of pneu matosis intestinalis was seen. The remainder of the CT, including the gallbladder, appeared normal (Figure 2). After confirming these findings with two board-certified radiologists, the patient was taken immediately to the opera ting room for exploratory laparotomy. The entire small bowel, colon, and rectum appeared grossly normal. The gallbladder appeared distended and necrotic; it was therefore removed. Pathologically, the gallbladder showed *Cryptosporidium Parvum* (Figure 3). The patient had an uneventful post-operative course. However, given the ad vanced nature of her AIDS and her poor functional status, she was discharged home with hospice services eight days after surgery.

DISCUSSION

HPVG occurs when intraluminal gas enters the porto-

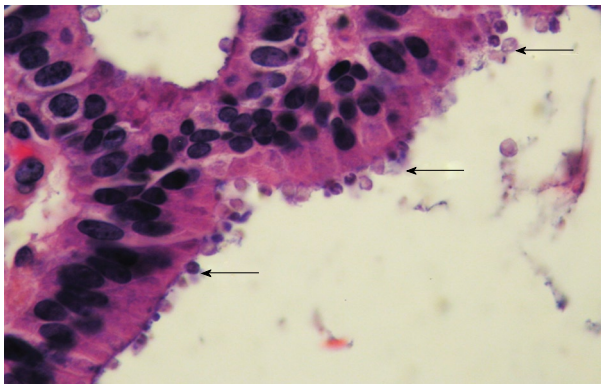


Figure 3 Gallbladder showing *Cryptosporidium* located on the surface of the epithelium.

mesenteric venous circulation as a consequence of mucosal damage from bowel ischemia, inflammatory bowel disease, bowel distention, intra-abdominal infection, or peptic ulcer disease. In some instances, the proliferation of non-pathogenic gas-forming bacteria in the lumen can lead to the radiographic findings of pneumatosis intestinalis and subsequently HPVG. Similarly, increased intraluminal pressure during colonoscopy or intraperitoneal pressure associated with blunt trauma can also permit bowel gas to gain access to the portal venous circulation through microscopic mucosal injury[3-11].

Intra-abdominal infections associated with HPVG include diverticulitis, abdominal abscesses, cholycystitis, cholangitis, appendicitis, and colitis[4,12-15]. The pathogenesis of infectious HPVG is not fully understood. Some theories include septicemia in branches of the mesenteric and portal veins[16], increased carbohydrate fermentation due to bacteria in the intraluminal region, or a mesocolic abscess causing infra-mesocolic perforation, allowing gas to access to the portal vasculature[17]. Furthermore, the coexistence of a chronic disease, such as renal failure, diabetes mellitus or hypertension can predispose to HPVG by altering the intestinal microbial flora[18].

Cryptosporidium spp. is a major cause of gastrointestinal disease in both immunocompetent and immunodeficient individuals. Although these infections are typically self-limited in healthy individuals, they can have severe manifestations in immunocompromised patients, particularly those with AIDS[19]. When cryptosporidiosis presents as disseminated disease, there can be involvement of the small intestine, colon, biliary tract, pancreas, and the respiratory tract. Of patients with intestinal cryptosporidiosis, ten percent have biliary tract abnormalities[20-21]. The risk of fecal carriage, severity of illness, and development of severe complications of cryptosporidiosis are inversely related to the CD4 count[19]. Our patient had a CD4 count of 12, which placed her at a very high risk of complicated infection. To our knowledge, AIDS-related cryptosporidiosis as a cause for HPVG has not been reported.

In conclusion, the clinical significance of HPVG is variable, and it depends primarily on the underlying pathology. In the most severe conditions it can be the result of mesenteric ischemia; however, growing literature is showing that there are less catastrophic conditions in which HPVG may occur. We conclude that in a patient with AIDS, *Cryptosporidium* can cause HPVG. This case illustrates another cause of HPVG that should be considered in patients with AIDS.

REFERENCES

1 **Liebman PR**, Patten MT, Manny J, Benfield JR, Hechtman HB. Hepatic--portal venous gas in adults: etiology, pathophysiology and clinical significance. *Ann Surg* 1978; **187**: 281-287

2 **Muscari F**, Suc B, Lagarrigue J. [Hepatic portal venous gas: is it always a sign of severity and surgical emergency?]. *Chirurgie* 1999; **124**: 69-72

3 **Draghetti MJ**, Salvo AF. Gas in the mesenteric veins as a nonfatal complication of diverticulitis: report of a case. *Dis Colon Rectum* 1999; **42**: 1497-1498

4 **Sen M**, Akpinar A, Inan A, Sişman M, Dener C, Akin K. Extensive hepatic-portal and mesenteric venous gas due to sigmoid diverticulitis. *World J Gastroenterol* 2009; **15**: 879-881

5 **Katz BH**, Schwartz SS, Vender RJ. Portal venous gas following a barium enema in a patient with Crohn's colitis. A benign finding. *Dis Colon Rectum* 1986; **29**: 49-51

6 **Pappas D**, Romeu J, Tarkin N, Dave PB, Messer J. Portal vein gas in a patient with Crohn's colitis. *Am J Gastroenterol* 1984; **79**: 728-730

7 **Sadhu VK**, Brennan RE, Madan V. Portal vein gas following air-contrast barium enema in granulomatous colitis: report of a case. *Gastrointest Radiol* 1979; **4**: 163-164

8 **Ng SS**, Yiu RY, Lee JF, Li JC, Leung KL. Portal venous gas and thrombosis in a Chinese patient with fulminant Crohn's colitis: a case report with literature review. *World J Gastroenterol* 2006; **12**: 5582-5586

9 **Abboud B**, El Hachem J, Yazbeck T, Doumit C. Hepatic portal venous gas: physiopathology, etiology, prognosis and treatment. *World J Gastroenterol* 2009; **15**: 3585-3590

10 **Wiot JF**, Felson B. Gas in the portal venous system. *Am J Roentgenol Radium Ther Nucl Med* 1961; **86**: 920-929

11 **Niki M**, Shimizu I, Horie T, Okazaki M, Shiraishi T, Takeuchi H, Fujiwara S, Murata M, Yamamoto K, Iuchi A, Atagi Y, Ito S. Hepatic portal venous gas disappearing within 24 hours. *Intern Med* 2002; **41**: 950-952

12 **Dennis MA**, Pretorius D, Manco-Johnson ML, Bangert-Burroughs K. CT detection of portal venous gas associated with suppurative cholangitis and cholecystitis. *AJR* 1985; **145**: 1017-1018

13 **Tuite DJ**, Byrne A, Colhoun E, Torreggiani WC. Pneumatosis intestinalis and portal-venous gas: an unusual presentation of acute appendicitis. *Australas Radiol* 2007; **51** Spec No.: B137-B139

14 **Bach MC**, Anderson LG, Martin TA Jr, McAfee RE. Gas in the hepatic portal venous system. A diagnostic clue to an occult intra-abdominal abscess. *Arch Intern Med* 1982; **142**: 1725-1726

15 **Hussain A**, Mahmood H, El-Hasani S. Portal vein gas in emergency surgery. *World J Emerg Surg* 2008; **3**: 21

16 **Yoshida M**, Mitsuo M, Kutsumi H, Fujita T, Soga T, Nishimura K, Kawabata K, Kadotani Y, Kinoshita Y, Chiba T, Kuroiwa N, Fujimoto S. A successfully treated case of multiple liver abscesses accompanied by portal venous gas. *Am J Gastroenterol* 1996; **91**: 2423-2425

17 **Current WL**, Reese NC. A comparison of endogenous development of three isolates of Cryptosporidium in suckling mice. *J Protozool* 1986; **33**: 98-108

18 **Chan SC**, Wan YL, Cheung YC, Ng SH, Wong AM, Ng KK. Computed tomography findings in fatal cases of enormous hepatic portal venous gas. *World J Gastroenterol* 2005; **11**: 2953-2955

19 **Sorvillo FJ**, Lieb LE, Kerndt PR, Ash LR. Epidemiology of cryptosporidiosis among persons with acquired immunodeficiency syndrome in Los Angeles County. *Am J Trop Med Hyg* 1994; **51**: 326-331
20 **Soave R**, Armstrong D. Cryptosporidium and cryptosporidiosis. *Rev Infect Dis* 1986; **8**: 1012-1023
21 **Cello JP**. Human immunodeficiency virus-associated biliary tract disease. *Semin Liver Dis* 1992; **12**: 213-218

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i11.410

World J Hepatol 2010 November 27; 2(11): 410-415
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

CASE REPORT

Acute liver injury induced by weight-loss herbal supplements

Gary C Chen, Vivek S Ramanathan, David Law, Pauline Funchain, George C Chen, Samuel French, Boris Shlopov, Viktor Eysselein, David Chung, Sonya Reicher, Binh V Pham

Gary C Chen, Vivek S Ramanathan, David Law, Pauline Funchain, George C Chen, Samuel French, Boris Shlopov, Viktor Eysselein, David Chung, Sonya Reicher, Binh V Pham, Department of Gastroenterology and Pathology, Harbor UCLA Medical Center, Torrance, CA 90509, United States
Author contributions: Chen Gary C, Ramanathan VS, Law D, Funchain P, and Chen George C were involved in direct patient care, data gathering, and case report write ups; French S and Shlopov B are from the department of pathology and interpreted the histology; and Eysselein V, Chung D, Reicher S and Pham BV were the attending gastroenterologists supervising background research and validity.
Supported by Harbor UCLA Medical Center and The Division of Gastroenterology
Correspondence to: Vivek S Ramanathan, MBChB, Department of Medicine, Division of Gastroenterology, Harbor UCLA Medical Center, 1000 W. Carson St, Torrance, CA 90502, United States. drvivekram@gmail.com
Telephone: +1-917-4340814 Fax: +1-562-9244890
Received: August 3, 2010 Revised: November 4, 2010
Accepted: November 11, 2010
Published online: November 27, 2010

Abstract

We report three cases of patients with acute liver injury induced by weight-loss herbal supplements. One patient took Hydroxycut while the other two took Herbalife supplements. Liver biopsies for all patients demonstrated findings consistent with drug-induced acute liver injury. To our knowledge, we are the first institute to report acute liver injury from both of these two types of weight-loss herbal supplements together as a case series. The series emphasizes the importance of taking a cautious approach when consuming herbal supplements for the purpose of weight loss.

© 2010 Baishideng. All rights reserved.

Key words: Hydroxycut; Herbalife; Hepatotoxicity; Herbal; Weight-loss

Peer reviewers: Mary Ko Manibusan, Co-Chair, US Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division - Crystal City, 8136 Viola Street, Springfield, VA 22152, United States; Ferruccio Bonino, Professor, Chief, Scientific Officer, Fondazione IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Via F. Sforza 28, Milano 20122, Italy

Chen GC, Ramanathan VS, Law D, Funchain P, Chen GC, French S, Shlopov B, Eysselein V, Chung D, Reicher S, Pham BV. Acute liver injury induced by weight-loss herbal supplements. *World J Hepatol* 2010; 2(11): 410-415 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i11/410.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i11.410

INTRODUCTION

We have seen a significant increase in the popularity and usage of over the counter herbal supplements over the past few years[1]. Unfortunately, the majority of these herbal supplements are not regulated by drug administrations worldwide. Many herbal supplements contain compounds that carry potentially severe side effects including hepatotoxicity. We report three cases of acute liver injury induced by weight-loss herbal supplements. Hydroxycut (MuscleTech, Mississauga, Ontario, Canada) (case 1) and Herbalife (Herbalife, Los Angeles, USA) (cases 2 and 3) supplements were the suspected culprits of acute liver injury. Hydroxycut is a popular dietary supplement consisting of a variety of herbal mixtures that claims to enhance the weight loss process[2]. Acute liver injury associated with Hydroxycut use has been previously reported, but only one case had liver biopsy data showing cholestasis and portal inflammation[3-6]. Similarly, Herbalife weight-loss dietary products are popular supplements consisting of a variety of herbal mixtures that claim to facilitate weight reduction[7]. Cases of acute liver injury after consumption of Herbalife products have been previously reported, with two patients developing fulminant liver failure requiring

liver transplantation. The first patient survived while the second died[8-11]. In all of our cases, we were able to demonstrate drug-induced acute liver injury on liver biopsy specimens.

CASE REPORT

Case 1

A 31-year-old woman presented to our hospital complaining of 2-wk history of fatigue, jaundice, and nausea. She denied any prior medical or surgical conditions, family history of liver disease, and acetaminophen or prescription medication use. She further denied history of blood transfusion, tattoo, alcohol use, or recreational drug use. She had been taking Hydroxycut for one year to enhance her weight loss. She had been taking the recommended dose of 2 tablets twice a day.

The patient was afebrile with normal hemodynamics upon presentation. Her physical examination was remarkable for generalized jaundice, scleral icterus, and mild upper quadrant tenderness to palpation without rebound or guarding. Initial laboratory studies were significant for serum aspartate aminotransferase (AST) level of 1407 U/L (normal range 15-41), serum alanine aminotransferase (ALT) level of 1278 U/L (normal range 7-35), serum alkaline phosphatase of 256 U/L (normal range 38-126), serum total bilirubin (TB) of 7.1 mg/dL (normal range 0.2-1.2), and international normalized ratio (INR) of 1.3 I/U (normal range 0.8-1.2). Given these findings, patient was admitted to the hospital for a higher level of care.

Standard blood tests were negative for hepatitis A, B, C, E, Ebstein Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within the normal range. Right upper quadrant ultrasound showed diffuse echogenicity of the liver. Liver biopsy was performed and showed multi-lobular necrosis consistent with acute toxic necrosis and fulminant hepatitis (Figure 1).

The patient's liver function tests peaked 4 d after admission with serum AST level of 1613 U/L, ALT level of 1227 U/L, serum alkaline phosphatase of 268 U/L, serum TB of 10.5 mg/dL, and INR staying at 1.3 I/U. She did not develop evidence of hypoglycemia or portal-systemic encephalopathy. Her jaundice and scleral icterus resolved over the following 2-wk. Her liver tests gradually improved within the following few months.

Case 2

A 37-year-old woman presented to our hospital with a 1-mo history of diffuse abdominal pain, mild nausea, and painless jaundice. She denied any past medical or surgical history, family history of liver disease, or any alcohol or illicit substance abuse. She admitted that she had been taking Herbalife dietary supplements for the past 3-mo in an attempt to lose weight. Her Herbalife regimen consisted of the Formula One Nutritional Shake Mix, the Multivitamin Complex, the Cell Activator, the Cell-U-Loss, the Herbal Concentrate Original, and the Total Control formula.

The patient was afebrile with normal vital signs on presentation. Her physical exam was noticeable for bilateral scleral icterus and generalized jaundice. Her abdominal exam revealed a non-tender, non-distended abdomen with no stigmata of liver disease. Initial laboratory studies were significant for an AST level of 2199 U/L, serum ALT level of 2068 U/L, serum alkaline phosphatase of 185 U/L, and TB of 15.3 mg/dL. All other laboratory values, including amylase, lipase, and INR, were within normal limits. Given these lab abnormalities, the patient was admitted to the hospital for further work-up.

Standard blood tests were negative for hepatitis A, B, C, E, EBV, CMV, HIV, antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within normal range. A computerized tomography (CT) scan of the abdomen and pelvis with intravenous (IV) contrast showed multiple low-density lesions in the liver measuring up to 8-mm. A liver biopsy revealed acute necrotizing hepatitis both centrolobular and periportal, consistent with a drug-induced etiology (Figure 2). However, her liver biopsy specimens also showed evidence of bridging fibrosis, which suggest some degree of chronic liver disease but with drug-induced injury in addition.

The patient was treated supportively with fluids and nutrition. Her liver tests steadily declined from the day of admission and on hospital day 8 (day of discharge) her liver tests revealed a AST level of 1788 U/L, ALT level of 1501 U/L, and serum alkaline phosphatase of 183 U/L. The only laboratory value to increase was the patient's serum TB, which was at 29.9 mg/dL on discharge. The patient did not develop encephalopathy, hypoglycemia, or any other complications. The patient was followed for several months, throughout which her symptoms continued to improve.

At her 2-mo follow-up, the patient's icterus and jaundice had resolved completely. Her labs at this time showed a serum AST level of 51 U/L, serum ALT level of 43 U/L, serum alkaline phosphatase of 65 U/L, and serum TB of 1.1 mg/dL.

Case 3

A 53-year-old previously healthy woman presented with a 3-wk history of painless jaundice and pruritus. She denied any family history of liver disease, or any alcohol or illicit substance abuse. She had not been taking any new prescribed medications. On further questioning about over-the-counter supplements she divulged a 4-mo history of consuming various Herbalife weight loss products in the form of shakes, teas and pills.

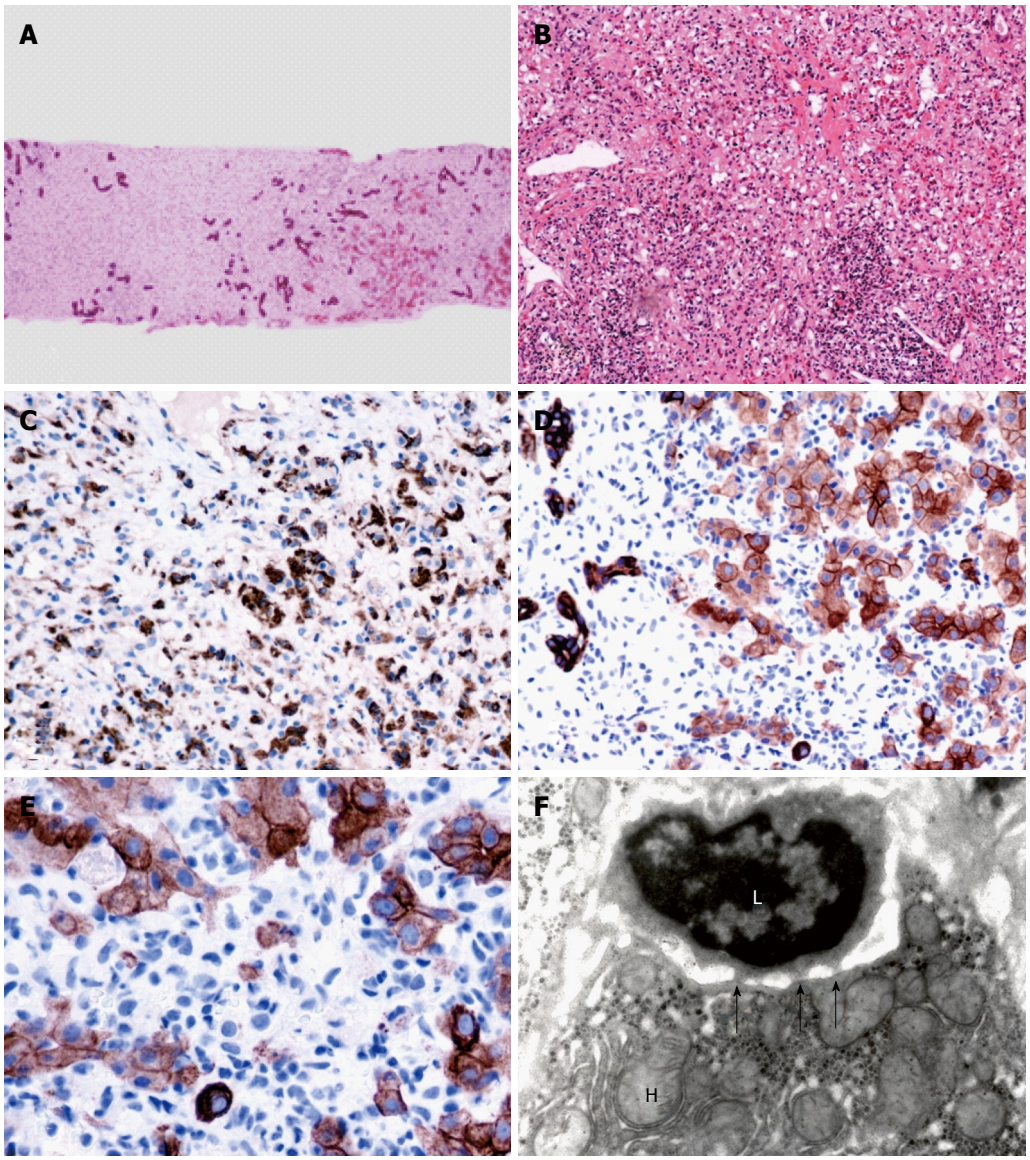


Figure 1 Liver biopsy showed extensive patchy areas of multilobular necrosis with only bile ducts remaining, extensive ductal metaplasia, severe lymphocytic and macrophages in filtration of portal tracts and lobular parenchyma and patchy plasma cell infiltrates. Histological changes were consistent with acute troxis necrosis and fulminant hepatitis. A: Liver lobules showing massive necrosis with only bile ducts remaining (hematoxiline and eosin stain × 52); B: Lymphocytic infiltration of portal tract and lobular parenchyma (hematoxiline and eosin stain × 130); C: Liver lobular necrosis with macrophages cleaning the debris (CD68 stain × 130); D: Ductal metaplasia. Lymphocytic infiltration in the sinusoids (CAM5.2 stain × 260); E: High power, lymphocytes destroying hepatocytes (CAM5.2 stain × 520); F: Lymphocyte "eating" hepatocytes in a liver parenchyma (troxis necrosis), arrow showing immunological synapses (Electron microscopy × 15000).

On physical exam the patient's vital signs were within normal limits. On general inspection she had scleral icterus and jaundice, with evidence of excoriations. A 2-cm palpable liver edge could be appreciated, that was tender to touch. There were no other signs of chronic liver disease. Initial laboratory values revealed a hepatocellular pattern of injury, with an AST of 1282 U/L, ALT of 983 U/L, and alkaline phosphatase of 292 U/L, with a TB of 18.2 mg/dL. An ultrasound showed borderline hepatomegaly of 17-cm.

Standard blood tests for hepatitis A, B, C, E, EBV, CMV, HIV, antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, alpha-1-antitrypsin deficiency, and anti-mitochondrial antibody were negative. Serum acetaminophen and urine toxicity screens were negative. Serum ceruloplasmin, ferritin, iron studies, and immunoglobulins were all within normal range.

Liver biopsy was performed and showed cholestasis, consistent with drug induced hepatitis (Figure 3). 2-mo after complete abstinence from the Herbalife supplements her jaundice resolved, as did her liver tests.

DISCUSSION

Acute liver injury induced by over the counter weight-loss herbal supplement Hydroxycut and Herbalife products have been reported previously[3-6,8-11]. These case reports were limited by the fact that liver biopsies were performed in only a few patients, confirming clinical suspicions histologically. In terms of our patients, all three had liver biopsy performed and all showed some common morphological features including diffuse lymphocytic infiltration of sinusoids and portal tracts, ductal metaplasia and toxic necrosis. Some variations of morphological features could be explained by predominance of intrinsic or idiosyncratic mechanisms of hepatic injury, individual patient response to the affecting drug and duration of injury. The patients' liver biopsy specimens were stained with periodic acid-Schiff (PAS) stain with diastase. No hyaline globules were identified in any of the three cases. The absence of histological findings and the fact that our patients had no history of chronic obstructive pulmonary disease excluded diagnosis of alpha-1-antitripsin deficiency in all three

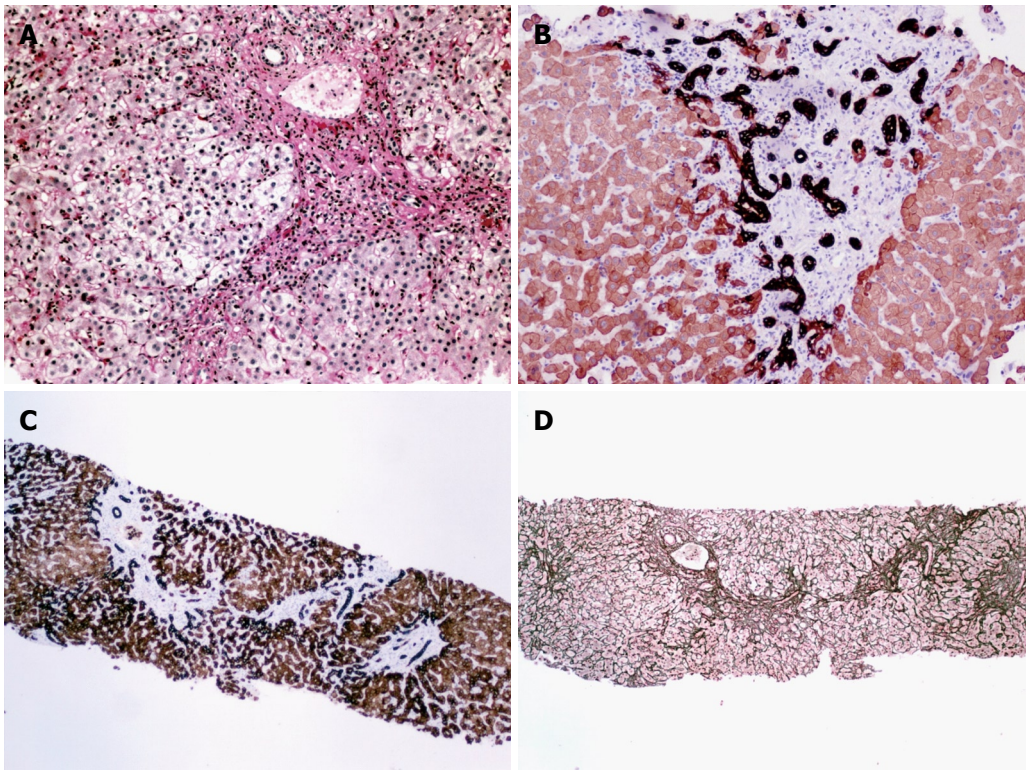


Figure 2 Liver biopsy was performed and showed pe riportal bridging fibrosis, ductal metaplasia, cholestasis, moderate intralobular lymphocytic infiltration, and troxis necrosis and ap optosis consistent with dr ug-induced hepatitis on top chronic liver disease. A: Li ver showing periportal fibro sis and cholestasis (periodic acid-Schiff stain × 130); B: Portal tract showing duc tal metaplasia and peripor tal fibrosis (AE1/AE3 stain × 260); C: Portal - portal bridging fibrosis (CAM5.2 stain × 52); D: Portal - portal bridging fibrosis (Reticu lin stain × 52).

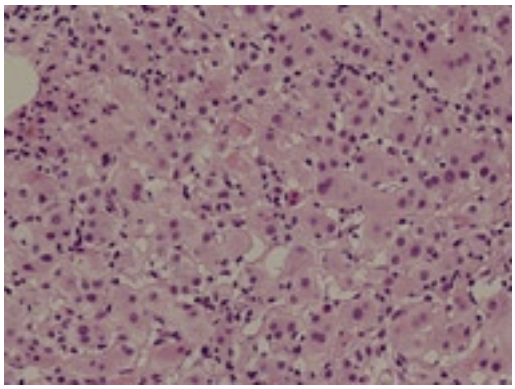


Figure 3 A liver biopsy revealed acute hepatitis characterized by hepatocellular injury, with periportal fibrosis, cholestasis, ductal metaplasia and diffuse intralobular and periportal troxis necrosis consistent with a drug-induced etiology. Intralobular lymphocytic infiltration. Arrow showing apoptosis of hepatocytes (hematoxiline and eosin stain × 260).

cases. Prussian blue and copper stains did not reveal excessive iron or copper depositions in the hepatocytes and Kupffer cells.

Only one previous case of Hydroxycut-induced acute liver injury had reported findings on liver biopsy. Although the most likely explanation for the mechanism of liver injury caused by these herbal products is idiosyncratic reaction, one of the ingredients in Hydroxycut, green tea extract (*Camellia sinensis*), has been linked with acute liver injury in other over the counter weight-loss herbal supplements[12-20]. In fact, the weight-loss herbal supplement Exolise (Arkopharma, Carros, France), which also contained *C. sinensis*, was withdrawn from the market because it was linked to multiple cases of liver injury[13]. Furthermore, several cases of hepatotoxicity were associated with another herbal weight-loss supplement, Cuur (Scandinavian Clinical Nutrition, Sweden), which also contains the ethanolic dry extract of green tea (*C. sinensis*)[15]. Rechallenging patients with the same product led to hepatotoxicity, confirming the role of *C. sinensis*[12,16]. In all reported cases of acute liver injury induced by Hydroxycut, patients' liver function tests recovered over time following cessation of the product. However, there have been cases of liver failure caused by green tea extract *C. sinensis,* requiring orthotopic liver transplantation[13,16].

The liver biopsy obtained in our patient who took Hydroxycut showed multi-lobular necrosis consistent with acute toxic necrosis and fulminant hepatitis. These findings are similar to the findings in patients with liver injury associated with green tea extract *C. sinensis*, where prominent necrosis with inflammatory reaction is the hallmark presentation[15,16].

The exact mechanism of hepatotoxicity induced by Hydroxycut is unknown. However, as this product contains green tea extract *C. sinensis*, it is possible that this may play a role in acute liver injury caused by Hydroxycut. Prior investigation into the mechanism of hepatotoxicity by green tea extract was inconclusive[21]. Others have hypothesized that a possible allergic reaction to the green tea extract, contamination during the production of the extract or a metabolic idiosyncrasy are possible mechanisms of liver injury in these patients[16].

Both of our patients took several Herbalife weight-loss herbal products concurrently, similar to most of the previously reported cases of hepatotoxicity due to Herbalife products[8-11]. Therefore, it is difficult to identify the exact ingredient or mechanism that causes the liver injury, as in the previously documented cases[8-11]. In a previously reported case, one investigator was able to isolate contami-

nation with *Bacillus subtilis*, in which the bacterial supernatant caused dose-dependent increase of LDH leakage in HepG2 cells[8]. Although not commonly known as a human pathogen, *B. subtiliis* has been reported to cause food poisonings and a case of cholangitis in an immunocompromised patient[22-23]. Investigators have also suggested that another explanation for hepatotoxicity due to Herbalife products could be secondary to locally restricted contamination with chemicals such as softeners, preservatives, flavor enhancers, pesticides, or heavy metals either intentionally added during the production process or contained in the unrefined raw herb extracts[24].

To date, Herbalife has refused to provide detailed analyses of their products' composition and ingredients[25]. This contamination hypothesis could also explain the different patterns of pathology seen on liver biopsy specimens previously observed in patients with hepatotoxicity from Herbalife products as both predominantly cholestatic injury pattern and acute hepatitis pattern have been reported[8-11]. Our patients had findings consistent with acute hepatitis due to drug-induced liver injury on their liver biopsy specimens.

Due to the obesity epidemic, the usage of weight-loss herbal supplements has flourished. Green tea extract is one of the key components in many of the over-the-counter weight-loss herbal supplements. Although significant liver injury induced by herbal supplements taken for weight loss purposes is a rare event, we cannot ignore the fact that there have been multiple reported cases in the medical literature of hepatotoxicity associated with weight-loss herbal supplements including Hydroxycut and Herbalife products. Even though our patients successfully recovered from the adverse reactions, we must bear in mind that the hospitalization and medical care of these patients were associated with significant cost and healthcare resource utilization, while there is no evidence that herbal supplements can help with weight-loss[26]. We must also consider the impact on patients with underlying chronic liver disease, in whom herbal weight loss medications could cause worsening in their synthetic function and even fulminant failure. In May of 2009, the US Food and Drug Administration warned consumers to immediately stop using Hydroxycut products, citing linkage to liver damage in one patient who died due to liver failure[27]. However, Hydroxycut products are currently still available in many parts of the world. Likewise, Herbalife products are widely available globally. Therefore, it is these authors' view that closer monitoring of patients taking weight-loss herbal supplements as well as tighter regulation from government drug agencies is warranted. Furthermore, our cases once again demonstrated the importance of questioning patients regarding the usage of herbal or nutritional supplements at the time of evaluation.

REFERENCES

1 **Kelly JP**, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. *Arch Intern Med* 2005; **165**: 281-286

2 Supplemental facts and ingredients. Available from: URL: http://www.hydroxycut.com/products/hydroxycut/index.shtml

3 **Stevens T**, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. *Ann Intern Med* 2005; **142**: 477-478

4 **Jones FJ**, Andrews AH. Acute liver injury associated with the herbal supplement hydroxycut in a soldier deployed to Iraq. *Am J Gastroenterol* 2007; **102**: 2357-2358

5 **Shim M**, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. *Dig Dis Sci* 2009; **54**: 406-4088

6 **Dara L**, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. *World J Gastroenterol* 2008; **14**: 6999-7004

7 Supplemental facts and ingredients. Available from: URL: http://products.herbalife.com/weight-management

8 **Stickel F**, Droz S, Patsenker E, Bögli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with Bacillus subtilis. *J Hepatol* 2009; **50**: 111-117

9 **Elinav E**, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, Broide E, Ackerman Z, Kaluski DN, Lev B, Shouval D. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007; **47**: 514-520

10 **Schoepfer AM**, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J, Zimmermann A, Oneta CM. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol* 2007; **47**: 521-526

11 **Duque JM**, Ferreiro J, Salgueiro E. Hepatotoxicity associated with the consumption of herbal slimming products. *Med Clin (Barc)* 2007; **128**: 238-239

12 **Bonkovsky HL**. Hepatotoxicity associated with supplements containing Chinese green tea (Camellia sinensis). *Ann Intern Med* 2006; **144**: 68-71

13 **Gloro R**, Hourmand-Ollivier I, Mosquet B, Mosquet L, Rousselot P, Salamé E, Piquet MA, Dao T. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. *Eur J Gastroenterol Hepatol* 2005; **17**: 1135-1137

14 **Jimenez-Saenz M**, Martinez-Sanchez C. Green tea extracts and acute liver failure: the need for caution in their use and diagnostic assessment. *Liver Transpl* 2007; **13**: 1067

15 **Bjornsson E**, Olsson R. Serious adverse liver reactions associated with herbal weight-loss supplements. *J Hepatol* 2007; **47**: 295-297; author reply 297-298

16 **Molinari M**, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, Nashan B, Peltekian K. Acute liver failure induced by green tea extracts: case report and review of the literature. *Liver Transpl* 2006; **12**: 1892-1895

17 **Thiolet C**, Mennecier D, Bredin C, Moulin O, Rimlinger H, Nizou C, Vergeau B, Farret O. [Acute cytolysis induced by Chinese tea]. *Gastroenterol Clin Biol* 2002; **26**: 939-940

18 **Vial T**, Bernard G, Lewden B, Dumortier J, Descotes J. Acute hepatitis due to Exolise, a Camellia sinensis dried ethanolic extract [letter]. *Med Clin (Barc)* 2003; **121**: 598-599

19 **García-Morán S**, Sáez-Royuela F, Gento E, López Morante A, Arias L. Acute hepatitis associated with Camellia thea and Orthosiphon stamineus ingestion [letter]. *Gastroenterol Hepatol* 2004; **27**: 559-560

20 **Porcel JM**, Bielsa S, Madronero AB. Hepatotoxicity associated with green tea extracts [electronic letter]. Accessed by www.annals.org on June 3, 2005

21 **Schmidt M**, Schmitz HJ, Baumgart A, Guédon D, Netsch MI, Kreuter MH, Schmidlin CB, Schrenk D. Toxicity of green tea extracts and their constituents in rat hepatocytes in primary culture. *Food Chem Toxicol* 2005; **43**: 307-314

22 **Kramer JM**, Gilbert RJ. Bacillus cereus and other Bacillus species. In: Doyle MP, editor. Foodborne bacterial pathogens. New York: Decker, 1989: 21-70

23 **Wallet F**, Crunelle V, Roussel-Delvallez M, Fruchart A, Saunier P, Courcol RJ. Bacillus subtilis as a cause of cholangitis in polycystic kidney and liver disease. *Am J Gastroenterol* 1996; **91**: 1477-1478
24 **De Smet PA**. Herbal remedies. *N Engl J Med* 2002; **347**: 2046-2056
25 **Stickel F**. Slimming at all costs: Herbalife-induced liver injury. *J Hepatol* 2007; **47**: 444-446
26 **Lenz TL**, Hamilton WR. Supplemental products used for weight loss. *J Am Pharm Assoc (2003)* 2004; **44**: 59-67; quiz 67-68
27 Available from: URL: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm152152.htm

S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i11.416

World J Hepatol 2010 November 27; 2(11): 416-418
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

CASE REPORT

Hepatocellular carcinoma, with portal thrombus after viral eradication, disappeared by 5-fluorouracil and interferon

Tomofumi Miura, Nobuaki Suzuki, Junichiro Nakamura, Satoshi Yamada, Tsutomu Miura, Masahiko Yanagi, Hiroyuki Usuda, Iwao Emura, Toru Takahashi

Tomofumi Miura, Nobuaki Suzuki, Junichiro Nakamura, Satoshi Yamada, Tsutomu Miura, Masahiko Yanagi, Toru Takahashi, Division of Gastroenterology and Hepatology, Nagaoka Red Cross Hospital, 2-297-1, Senshu, Nagaoka, Niigata 940-2085, Japan
Hiroyuki Usuda, Division of Medical Technology, Nagaoka Red Cross Hospital, 2-297-1, Senshu, Nagaoka, Niigata 940-2085, Japan
Iwao Emura, Division of Pathology, Nagaoka Red Cross Hospital, 2-297-1, Senshu, Nagaoka, Niigata 940-2085, Japan
Author contributions: Miura T, Suzuki N, Nakamura J, Yamada S, Miura T, Yanagi M and Takahashi T wrote the paper; and Usuda H and Emura I engaged in the pathological examination of the patient.
Correspondence to: Tomofumi Miura, MD, Division of Gastroenterology and Hepatology, Nagaoka Red Cross Hospital, 2-297-1, Senshu, Nagaoka, Niigata 940-2085, Japan. miuratom@nagaoka.jrc.or.jp
Telephone: +81-258-283600 Fax: +81-258-289000
Received: May 18, 2010 Revised: November 5, 2010
Accepted: November 12, 2010
Published online: November 27, 2010

Abstract

Hepatocarcinogenesis after a sustained virological response (SVR) in type C chronic hepatitis and cirrhosis is an important issue in endemic areas; hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) therapy is especially very hard. We herein report a first case in which combination therapy with interferon-α and continuous intra-arterial infusion of 5-fluorouracil (designated as FAIT) provided a complete response in HCC with PVTT after SVR. Therefore, we think that FAIT is a good option to treat HCC with or without PVTT, even after SVR.

© 2010 Baishideng. All rights reserved.

Key words: Hepatocellular carcinoma; Portal vein tumor thrombus; Sustained virological response; 5-Fluorouracil intra-arterial infusion

Peer reviewers: Johanna Kassiani Delladetsima, Associate Professor, Department of Pathology, Medical School, University of Athens, 75 Mikras Asias Str., Goudi, Athens 11527, Greece; Pierce Kah-Hoe Chow, Associate Professor, Department of General Surgery, Singapore General Hospital, Singapore 169608, Singapore

Miura T, Suzuki N, Nakamura J, Yamada S, Miura T, Yanagi M, Usuda H, Emura I, Takahashi T. Hepatocellular carcinoma, with portal thrombus after viral eradication, disappeared by 5-fluorouracil and interferon. *World J Hepatol* 2010; 2(11): 416-418 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i11/416.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i11.416

INTRODUCTION

Hepatocarcinogenesis after a sustained virological response (SVR) in type C chronic hepatitis and cirrhosis is an important issue in endemic areas. On the other hand, hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) therapy is especially known to be very hard. There has never been a sufficient therapeutic option in PVTT without a miserable prognosis. We herein report a first case in which combination therapy with interferon-α and continuous intra-arterial infusion of 5-fluorouracil (designated as FAIT) provided a complete response in HCC with PVTT after SVR.

CASE REPORT

A 69-year-old man was having a periodical check-up for chronic hepatitis C in our outpatient clinic. In 2006, a SVR was achieved by pegylated interferon α-2b with ribavirin for 48 wk. HCC 17 mm in size occurred in the caudate lobe 18 mo after SVR and a caudate lobectomy was performed. The extirpated lobe contained hepatocellular carcinoma, Edmondson's grade Ⅲ, pT3N0M0. Liver histology was macronodular cirrhosis. Adjuvant chemo-

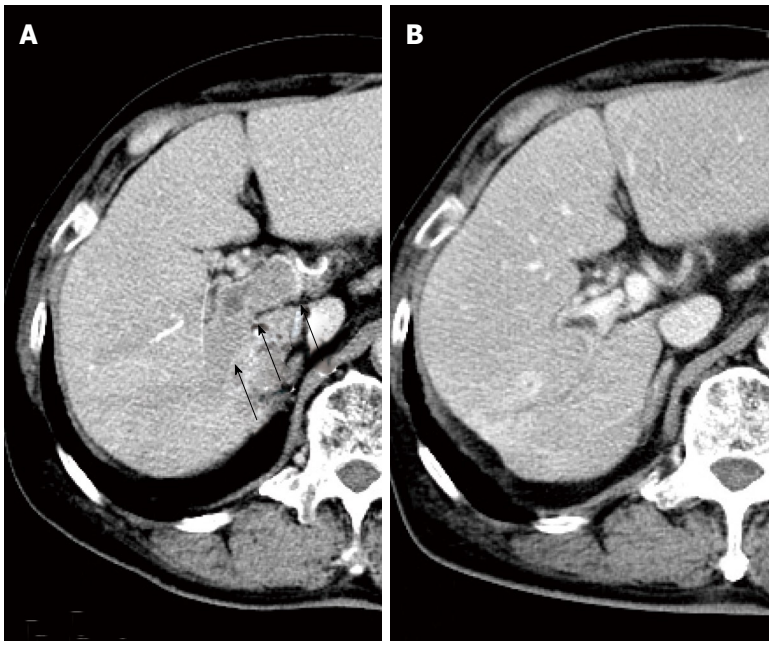


Figure 1 Abdominal computed tomography. A: Portal vein tumor thrombus (PVTT) extends to the major trunk (arrows) before intra-arterial infusion of 5-FU (FAIT); B: After four courses of FAIT, PVTT clearly disappeared and the portal vein becomes vacant.

therapy was recommended since the surgical margin was positive for cancer cells. However, he rejected our proposal and thus, he chose just periodical check-ups in our outpatient clinic.

Six months after surgery, HCC recurred at the resection margin with PVTT that extended to the major trunk (Vp4) in computed tomography (CT) (Figure 1A). His preserved liver function was Child-Pugh score 5, thus classified as grade A.

He was treated with combination therapy with interferon (IFN)-α and continuous intra-arterial infusion of 5-FU (FAIT). IFN-α (6×10^6 U) was self-injected intramuscularly on day 1, 3 and 5 in each week. Five-FU (500 mg/m^2 per day for 2 wk) was continuously infused through the proper hepatic artery *via* a catheter connected to a subcutaneously implanted drug delivery system every 4 wk[1,2]. A severe adverse event of grade 3 oral mucositis (according to the Common Terminology Criteria for Adverse Events v3.0) appeared. Thus, 5-FU was reduced to 350 mg/m^2 per day in the second course with no severe adverse events thereafter. Elevated tumor markers (AFP and PIVKA-Ⅱ) fell under the upper normal limit after three courses and CT showed neither HCC nor PVTT after four courses of FAIT (Figure 1B). He is now having subsequent courses of FAIT without recurrence.

DISCUSSION

Chronic hepatitis C is now a curative disease by IFN therapy with ribavirin. The effects of IFN are summarized as follows: (1) elimination of HCV; (2) reduction of hepatic inflammation; (3) improvement in liver fibrosis; and (4) reduction in hepatocarcinogenesis[3,4].

Recently, a new issue, hepatocarcinogenesis after SVR, is emerging. In fact, it is reported that the hepatocarcinogenesis after SVR occurs in 1.5%, 2.4% and 4.1% at 5, 10 and 15 years respectively[5]. Cirrhosis, age over 50 and male are risk factors for hepatocarcinogenesis[5]. The present case had all three.

HCC is now treated according to the guideline[6]. Nevertheless, HCC with PVTT has a poor prognosis. Even in such circumstances, FAIT is effective in cases[1] and also as adjuvant chemotherapy[2]. The rationale of FAIT therapy includes: (1) IFN-α stimulates the metabolic activation of 5-FU[7]; and (2) the combination of IFN-α and 5-FU induces tumor cell apoptosis more than 5-FU alone[8]. IFN-α/β receptor[9] and type 1 interferon receptor[10] are correlated with the sensitivity to FAIT. Insulin-like growth factor-binding protein 7 (IGFBP7)[11], vascular endothelial growth factor (VEGF) signaling[12] and Wnt/β-catenin signaling pathway[13] are reported to be correlated with both the sensitivity and the antitumor effects. FAIT is a relatively novel therapeutic strategy. There is a clinical question whether HCC even after SVR maintains the sensitivity to IFN. On the other hand, the therapeutic strategy for HCC with PVTT after SVR has not been discussed enough in previous studies[1,2,10,14-18]. Hence the accumulation of related cases, clinical trials and the elucidation of more detailed mechanisms of actions in anti-tumor agents are needed in the near future.

In conclusion, FAIT showed a complete response for a case with HCC with PVTT after SVR. No previous report is currently available concerning this issue. HCC developed after SVR is now increasing in number and FAIT may be an option to treat HCC with or without PVTT, even after SVR, although further study is still needed.

REFERENCES

1 **Sakon M**, Nagano H, Dono K, Nakamori S, Umeshita K, Yamada A, Kawata S, Imai Y, Iijima S, Monden M. Combined intra-arterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002; **94**:

435-442
2 **Nagano** H, Miyamoto A, Wada H, Ota H, Marubashi S, Takeda Y, Dono K, Umeshita K, Sakon M, Monden M. Interferon-alpha and 5-fluorouracil combination therapy after palliative hepatic resection in patients with advanced hepatocellular carcinoma, portal venous tumor thrombus in the major trunk, and multiple nodules. *Cancer* 2007; **110**: 2493-2501
3 **Yoshida H**, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, Yamada G, Yokosuka O, Shiratori Y, Omata M. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterology* 2002; **123**: 483-491
4 **Nishiguchi S**, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346**: 1051-1055
5 **Hirakawa M**, Ikeda K, Arase Y, Kawamura Y, Yatsuji H, Hosaka T, Sezaki H, Akuta N, Kobayashi M, Saitoh S, Suzuki F, Suzuki Y, Kumada H. Hepatocarcinogenesis following HCV RNA eradication by interferon in chronic hepatitis patients. *Intern Med* 2008; **47**: 1637-1643
6 **Benson AB 3rd**, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D'Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdson ER, Sofocleous C, Vauthey JN, Venook AP, Goff LW, Yen Y, Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; **7**: 350-391
7 **Schwartz EL**, Hoffman M, O'Connor CJ, Wadler S. Stimulation of 5-fluorouracil metabolic activation by interferon-alpha in human colon carcinoma cells. *Biochem Biophys Res Commun* 1992; **182**: 1232-1239
8 **Horowitz RW**, Heerdt BG, Hu X, Schwartz EL, Wadler S. Combination therapy with 5-fluorouracil and IFN-alpha2a induces a nonrandom increase in DNA fragments of less than 3 megabases in HT29 colon carcinoma cells. *Clin Cancer Res* 1997; **3**: 1317-1322
9 **Kondo M**, Nagano H, Sakon M, Yamamoto H, Morimoto O, Arai I, Miyamoto A, Eguchi H, Dono K, Nakamori S, Umeshita K, Wakasa K, Ohmoto Y, Monden M. Expression of interferon alpha/beta receptor in human hepatocellular carcinoma. *Int J Oncol* 2000; **17**: 83-88
10 **Ota H**, Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Nakamura M, Damdinsuren B, Wada H, Marubashi S, Miyamoto A, Dono K, Umeshita K, Nakamori S, Wakasa K, Monden M. Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. *Br J Cancer* 2005; **93**: 557-564
11 **Tomimaru Y**, Eguchi H, Wada H, Noda T, Murakami M, Kobayashi S, Marubashi S, Takeda Y, Tanemura M, Umeshita K, Doki Y, Mori M, Nagano H. Insulin-like growth factor-binding protein 7 alters the sensitivity to interferon-based anticancer therapy in hepatocellular carcinoma cells. *Br J Cancer* 2010; **102**: 1483-1490
12 **Murakami M**, Kobayashi S, Marubashi S, Tomimaru Y, Noda T, Wada H, Eguchi H, Takeda Y, Tanemura M, Umeshita K, Doki Y, Mori M, Nagano H. Tyrosine Kinase Inhibitor PTK/ZK Enhances the Antitumor Effects of Interferon-alpha/5-Fluorouracil Therapy for Hepatocellular Carcinoma Cells. *Ann Surg Oncol* 2010; Epub ahead of print
13 **Noda T**, Nagano H, Takemasa I, Yoshioka S, Murakami M, Wada H, Kobayashi S, Marubashi S, Takeda Y, Dono K, Umeshita K, Matsuura N, Matsubara K, Doki Y, Mori M, Monden M. Activation of Wnt/beta-catenin signalling pathway induces chemoresistance to interferon-alpha/5-fluorouracil combination therapy for hepatocellular carcinoma. *Br J Cancer* 2009; **100**: 1647-1658
14 **Nagano H**. Treatment of advanced hepatocellular carcinoma: intra-arterial infusion chemotherapy combined with interferon. *Oncology* 2010; **78** Suppl 1: 142-147
15 **Nagano H**, Sakon M, Eguchi H, Kondo M, Yamamoto T, Ota H, Nakamura M, Wada H, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Dono K, Umeshit K, Nakamori S, Monden M. Hepatic resection followed by IFN-alpha and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. *Hepatogastroenterology* 2007; **54**: 172-179
16 **Obi S**, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S, Omata M. Combination therapy of intra-arterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006; **106**: 1990-1997
17 **Yamamoto T**, Nagano H, Imai Y, Fukuda K, Matsumoto H, Kondo M, Ota H, Nakamura M, Wada H, Noda T, Damdinsuren B, Dono K, Umeshita K, Nakamori S, Sakon M, Wakasa K, Monden M. Successful treatment of multiple hepatocellular carcinoma with tumor thrombi in the major portal branches by intra-arterial 5-fluorouracil perfusion chemotherapy combined with subcutaneous interferon-alpha and hepatectomy. *Int J Clin Oncol* 2007; **12**: 150-154
18 **Wada H**, Nagano H, Noda T, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Umeshita K, Dono K, Sakon M, Wakasa K, Monden M. Complete remission of hepatocellular carcinoma with portal vein tumor thrombus and lymph node metastases by arterial infusion of 5-fluorouracil and interferon-alpha combination therapy following hepatic resection. *J Gastroenterol* 2007; **42**: 501-506

S- Editor Zhang HN **L- Editor** Roemmele A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 November 27; 2(11): I
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

Acknowledgments to reviewers of *World Journal of Hepatology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Hepatology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Alex P Betrosian, MD, Third Department of Critical care, Athens University, Evgenidion Hopsital, 20 Papadiamantopoulou Str., Athens 11528, Greece

Ferruccio Bonino, Professor, Chief, Scientific Officer, Fondazione IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Via F. Sforza 28, Milano 20122, Italy

Stephen Lam Chan, MD, Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Street, Shatin, New Territories, Hong Kong, China

Pierce Kah-Hoe Chow, Associate Professor, Department of General Surgery, Singapore General Hospital, Singapore 169608, Singapore

Johanna Kassiani Delladetsima, Associate Professor, Department of Pathology, Medical School, University of Athens, 75 Mikras Asias Str., Goudi, Athens 11527, Greece

Radha Krishan Dhiman, MD, DM, FACG, Professor, Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

Joel Faintuch, MD, PhD, Department of Gastroenterology, Hospital das Clinicas, ICHC, 9th Floor, Room 9077, Sao Paulo 05403-900, Brazil

Toru Ishikawa, MD, Department of Gastroenterology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata 950-1104, Japan

Wan Yee Joseph Lau, MD, Professor, Clinical Sciences Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China

Qiang Liu, PhD, Vaccine and Infectious Disease Organization, University of Saskatchewan, 120 Veterinary Road, Saskatoon, Saskatchewan, S7N 5E3, Canada

Mary Ko Manibusan, Co-Chair, US Environmental Protection Agency, Office of Pesticide Programs, Health Effects Division - Crystal City, 8136 Viola Street, Springfield, VA 22152, United States

Zenichi Morise, MD, PhD, Department of Surgery, Fujita Health University School of Medicine, 1-98 Dengakugakubo Kutsukakecho, Toyoake, AICHI 470-1192, Japan

Emmanouil Sinakos, MD, Aristotle University of Thessaloniki, 11A, Perdika Str., Pilea 55535, Greece

Xun-Di Xu, MD, PhD, Department of Gastroenterological Surgery, Xiangya 2nd Hospital, Central South University, Renmin Zhong Road 139, Changsha 410011, Hunan Province, China

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 November 27; 2(11): I
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

Meetings

Events Calendar 2010

January 25-26
Tamilnadu, India
International Conference on Medical Negligence and Litigation in Medical Practice

January 25-29
Waikoloa, HI, United States
Selected Topics in Internal Medicine

January 26-27
Dubai, United Arab Emirates
2nd Middle East Gastroenterology Conference

March 04-06
Bethesda, MD, United States
8th International Symposium on Targeted Anticancer Therapies

March 05-07
Peshawar, Pakistan
26th Pakistan Society of Gastroenterology & Endoscopy Meeting

March 12-14
Bhubaneswar, India
18th Annual Meeting of Indian National Association for Study of the Liver

March 25-28
Beijing, China
The 20th Conference of the Asian Pacific Association for the Study of the Liver

March 27-28
San Diego, California, United States
25th Annual New Treatments in Chronic Liver Disease

April 07-09
Dubai, United Arab Emirates
The 6th Emirates Gastroenterology and Hepatology Conference, EGHC 2010

April 14-18
Vienna, Austria
The International Liver Congress™ 2010

May 01-05
New Orleans, LA, United States
Digestive Disease Week Annual Meeting

May 06-08
Munich, Germany
The Power of Programming: International Conference on Developmental Origins of Health and Disease

June 04-06
Chicago, IL, United States
American Society of Clinical Oncologists Annual Meeting

June 16-19
Hong Kong, China
ILTS: International Liver Transplantation Society ILTS Annual International Congress

September 10-12
Montreal, Canada
International Liver Association's Fourth Annual Conference

September 12-15
Boston, MA, United States
ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy Annual Meeting

September 16-18
Prague, Czech Republic
Prague Hepatology Meeting 2010

September 23-26
Prague, Czech Republic
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases

October 15-20
San Antonio, TX, United States
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting

October 23-27
Barcelona, Spain
18th United European Gastroenterology Week

October 29-November 02
Boston, Massachusetts, United States
The Liver Meeting® 2010--AASLD's 61st Annual Meeting

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2010 November 27; 2(11): I-V
ISSN 1948-5182 (online)
© 2010 Baishideng. All rights reserved.

Instructions to authors

GENERAL INFORMATION

World Journal of Hepatology (*World J Hepatol, WJH*, online ISSN 1948-5182, DOI: 10.4254), is a monthly, openaccess, peer-reviewed journal supported by an editorial board of 572 experts in hepatology from 45 countries..

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJH* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJH* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJH* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

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.

Name of journal

World Journal of Hepatology

CSSN

ISSN 1948-5182 (online)

Indexed and Abstracted in

PubMed Central

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical

method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJH* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interestsin relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Bo ok Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/1948-5182 office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjh@wjgnet.com, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJH*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5182/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A:...; B:...; C:...; D:...; E:...; F:...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation

content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn' s disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107115140.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and

on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/1948-5182/g_info_20100316080004.htm

Frontier: http://www.wjgnet.com/1948-5182/g_info_20100315103153.htm

Topic highlight: http://www.wjgnet.com/1948-5182/g_info_20100316080006.htm

Observation: http://www.wjgnet.com/1948-5182/g_info_20100107112630.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5182/g_info_20100315103748.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5182/g_info_20100315103829.htm

Review: http://www.wjgnet.com/1948-5182/g_info_20100107112834.htm

Original articles: http://www.wjgnet.com/1948-5182/g_info_20100107113351.htm

Brief articles: http://www.wjgnet.com/1948-5182/g_info_20100315104523.htm

Case report: http://www.wjgnet.com/1948-5182/g_info_20100107113649.htm

Letters to the editor: http://www.wjgnet.com/1948-5182/_info_20100107114003.htm

Book reviews: http://www.wjgnet.com/1948-5182/g_info_20100315105017.htm

Guidelines: http://www.wjgnet.com/1948-5182/g_info_20100315105107.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJH*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Hepatology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-59080038
Fax: +86-10-85381893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1948-5182/g_info_20100107114726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107114601.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJH will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

Authors of accepted articles must pay a publication fee.
EDITORIAL, TOPIC HIGHLIGHTS, BOOK REVIEWS and LETTERS TO THE EDITOR are published free of charge.