World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i14.4423

World J Gastroenterol 2015 April 14; 21(14): 4423-4426
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Six month abstinence rule for liver transplantation in severe alcoholic liver disease patients

Aiman Obed, Steffen Stern, Anwar Jarrad, Thomas Lorf

Aiman Obed, Anwar Jarrad, Hepatobiliary and Liver Transplant Unit, Jordan Hospital, Amman 11152, Jordan
Steffen Stern, Fakultät für Rechtswissenschaft, Universität Bielefeld, 33615 Bielefeld, Germany
Thomas Lorf, Georg-August-University Goettingen, D-37073 Gottingen, Germany
Author contributions: All authors contributed to data analysis and the interpretation of papers mentioned in this manuscript, as well as drafting the manuscript, making critical revisions, and giving final approval of the version to be published.
Conflict-of-interest: The authors declare no conflict of interest.

Correspondence to: Aiman Obed, MD FACS, FEBBS, Hepatobiliary and Liver Transplant Unit, Jordan Hospital, PO Box 520248, Amman 11152, Jordan. aimanobed@hotmail.com
Telephone: +962-6-4608080
Fax: +962-6-4607575
Received: November 29, 2014
Peer-review started: December 1, 2014
First decision: December 26, 2014
Revised: January 1, 2015
Accepted: January 30, 2015
Article in press: January 30, 2015
Published online: April 14, 2015

Abstract

Alcoholic liver disease (ALD) is the second most common diagnosis among patients undergoing liver transplantation (LT). The recovery results of patients transplanted for ALD are often at least as good as those of patients transplanted for other diagnoses and better than those suffering from hepatitis C virus, cryptogenic cirrhosis, or hepatocellular carcinoma. In the case of medically non-responding patients with severe acute alcoholic hepatitis or acute-on chronic liver failure, the refusal of LT is often based on the lack of the required alcohol abstinence period of six months. The obligatory abidance of a period of abstinence as a transplant eligibility requirement for medically non-responding patients seems unfair and inhumane, since the majority of these patients will not survive the six-month abstinence period. Data from various studies have challenged the 6-mo rule, while excellent survival results of LT have been observed in selected patients with severe alcoholic hepatitis not responding to medical therapy. Patients with severe advanced ALD should have legal access to LT. The mere lack of pre-LT abstinence should not be an obstacle for being listed.

Key words: Alcohol; Alcoholic hepatitis; Cirrhosis; Six month abstinence rule; Abstinence; Liver transplantation

Core tip: Severe alcoholic liver diseases that do not respond to medical therapy, such as alcoholic hepatitis or acute-on chronic liver failure, show life threatening one-year mortality rates of up to 90%. The majority of transplant centers demand 6-mo of alcohol abstinence prior to transplantation, the so-called "6-mo rule". This rule is void of scientific evidence and frequently the subject of controversial discussions. Since most patients with severe alcoholic liver disease will die before meeting the criteria of the 6-mo period of abstinence, liver transplantation has to be taken into account irrespective of the 6-mo abstinence period.

Obed A, Stern S, Jarrad A, Lorf T. Six month abstinence rule for liver transplantation in severe alcoholic liver disease patients. *World J Gastroenterol* 2015; 21(14): 4423-4426 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i14/4423.htm

DOI: http://dx.doi.org/10.3748/wjg.v21.i14.4423

TO THE EDITOR

We read the article "Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: An Italian position statement" by Testino *et al*[1] with particularly great interest.

In general, alcohol avoidance in patients with liver disease (especially in alcoholic liver cirrhosis) is advisable and medically beneficial[2,3], however patients suffering from either severe acute alcoholic hepatitis (SAAH) or acute-on chronic liver failure (ACLF) and not responding to medical therapy have high 3-mo mortality rates ranging from 60%-70%, and even reaching as high as 90% within the first year[4-7].

SAAH and ACLF are life-threating situations demanding intensive care unit (ICU) therapy. Typically, patients in such clinical conditions are already too sick to drink, with the vast majority failing to recover by stopping their consumption of alcohol[8-11].

Stadlbauer *et al*[12] revealed that patients who do not respond to medical therapy will inevitably die without a potentially lifesaving liver transplantation.

A recent study by Kumar *et al*[13] found that a change in MELD score at 2 wk was effective in determining the outcome. However, the study showed that an interval of 2 wk was sufficient to demonstrate an increased mortality or need for liver transplant in patients with ACLF.

Mathurin *et al*[6] presented a comparable conclusion regarding mortality prognosis of SAAH with an interval from 7 to 14 d after ICU admission. A lack of clinical improvement in patients with SAAH and ACLF during the first 2 wk of ICU treatment indicates a poor outcome or vital need for liver transplant.

The cornerstone for practicing evidence-based medicine is applying the best current knowledge to medical decision-making for each individual patient.

Unfortunately, with regard to the advanced end-stage ALD, current prejudices, barroom clichés, and public half-truths seem to overshadow the available evidence-based information.

The debatable 6-mo abstinence rule has not only been controversial ever since its introduction, but has also been harshly criticized and labeled as an unfair and inhumane rule with fatal consequences for ALD patients[14,15].

The available data questions the 6-mo rule whilst confirming well-known uncertainties about its ability and usefulness in predicting (heavy) alcohol relapse after LT[16-18].

Death or graft loss occurs in only about 4% of all ALD patients who experience a relapse of their disease. The most common causes of death in patients who continued to consume alcohol were cardiovascular events and cancer, not liver failure directly caused by alcohol consumption[1].

Data presented by Schmeding *et al*[19] in 2011 clearly indicates that ALD patients have better 5 and 10-year survival rates compared with HCV-infected patients, even in the case of alcohol relapse after liver transplantation.

Recently, Deruytter *et al*[20] observed recidivism of alcohol after liver transplantation in 29% of ALD patients and heavy drinking after LTX in 16%. More importantly, no significant difference in survival was found between non-relapsers, occasional drinkers, and problem drinkers.

Simultaneously, medical law experts are repetitively reminded, albeit from a different point of view than those in practical medicine, that constitutional law prohibits discrimination against subgroups and life differentiations as being either worthy or unworthy of life. They stress that the exclusion of non-sober ALD patients from being listed discriminated them and violated said constitutional law[21].

Considering that patients who experience acute liver failure after ecstasy consumption[22] or are suffering from acute hepatitis B infections due to careless sexual practices[23] have full access to the waiting list raises the question as to why patients with SAAH or ACLF should be treated any differently.

The United Network for Organ Sharing (UNOS) has still adopted the 6-mo rule, although it does advise that "exceptional" cases be referred to regional review boards for consideration.

The American Association for the Study of Liver Disease contemporary guidelines also advise 6 mo of zero alcohol consumption before LT, but they highlighted that this rule as it stands is not a defining factor as to whether or not a patient is accepted as a candidate for a liver transplant[24].

In the end, alcoholism has to be accepted as a disease that, in some cases, has a genetic background[25,26]. The lack of pre-transplant abstinence should not be considered as a justification for denying the legal right to have access to the liver transplantation waiting list for patients with advanced ALD[27].

Transplantation for alcoholic liver disease is prejudged, with its worthiness often being questioned due to the common misconception of ALD being regarded as a type of self-inflicted harm[28-30].

The segregation of patients with severe alcoholic cirrhosis who are considered to be proper candidates for LT after complete evaluation must be avoided[31].

Furthermore, the necessity of LT for ALD patients is generally misperceived and not taken seriously by general physicians or the general public. However, there are no moral or ethical arguments that could justify the exclusion of very ill patients with ALD from potentially lifesaving LT[32,33]. On the contrary, it would be considered a death sentence for these patients. The number of patients who have already passed away before they were even presented to a transplant

center remains unclear.

Treatment with artificial liver support devices has value in correcting major pathophysiological disturbances, and might be of individual help as a bridging procedure in patients with ACLF and SAAH until transplant[34-37].

In the end, the 6-mo rule is insufficient in predicting relapse risk after liver transplantation. Liver transplantation may be lifesaving in cases of advanced ALD or alcoholic hepatitis, but inflexible sobriety rules eliminate patients with a low risk of relapse from transplant consideration[38].

Lastly, it must be noted that the United Nations' Universal Declaration of Human Rights acknowledges that all human beings are born free and equal in terms of dignity and rights. Everyone has the right to life, liberty, security, and a standard of living adequate for the health and well-being of themselves and their family[39].

National transplant policy boards, patient support groups, and legislation clearly need to act and collaborate transparently and closely in regards to national constitutional law in order to educate the public and clarify that liver transplantation for advanced ALD is not a matter of medical scientific discussion, but rather a societal dilemma that has the potential to improve the life expectancy of many desperate patients.

We agree with all suggestions made by Testino *et al*[1], particularly with regard to efforts made to improve the screening of *de novo* tumors after liver transplantation and the prevention of cardiovascular complications, which are indeed required within the follow-up care in order to achieve further improvement for long-term outcome.

In summary, we conclude that the selection and allocation criteria for advanced end-stage ALD, especially the abstinence rule, should be appropriately revised to avoid further preventable patient death. In cases of SAAH and ACLF that do not respond to medical therapy 2 wk after admission, liver transplantation should be compulsory, regardless of achieved abstinence time.

REFERENCES

1 **Testino G**, Burra P, Bonino F, Piani F, Sumberaz A, Peressutti R, Giannelli Castiglione A, Patussi V, Fanucchi T, Ancarani O, De Cerce G, Iannini AT, Greco G, Mosti A, Durante M, Babocci P, Quartini M, Mioni D, Aricò S, Baselice A, Leone S, Lozer F, Scafato E, Borro P. Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: an Italian position statement. *World J Gastroenterol* 2014; **20**: 14642-14651 [PMID: 25356027 DOI: 10.3748/wjg.v20.i40.14642]

2 **Bendimerad P**, Blecha L. [Benefits in reducing alcohol consumption: how nalmefene can help]. *Encephale* 2014; **40**: 495-500 [PMID: 25454365 DOI: 10.1016/j.encep.2014.10.012]

3 **Shearn CT**, Petersen DR. Understanding the tumor suppressor PTEN in chronic alcoholism and hepatocellular carcinoma. *Adv Exp Med Biol* 2015; **815**: 173-184 [PMID: 25427907 DOI: 10.1007/978-3-319-09614-8_10]

4 **Addolorato G**, Mirijello A, Leggio L, Ferrulli A, D'Angelo C, Vassallo G, Cossari A, Gasbarrini G, Landolfi R, Agnes S, Gasbarrini A. Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. *Alcohol Clin Exp Res* 2013; **37**: 1601-1608 [PMID: 23578009 DOI: 10.1111/acer.12117]

5 **Donckier V**, Lucidi V, Gustot T, Moreno C. Reply to: "liver transplantation and severe acute alcoholic hepatitis: an ethical consideration". *J Hepatol* 2014; **61**: 707 [PMID: 24882053 DOI: 10.1016/j.jhep.2014.05.029]

6 **Mathurin P**, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011; **365**: 1790-1800 [PMID: 22070476 DOI: 10.1056/NEJMoa1105703]

7 **Abenavoli L**, Milic N, Rouabhia S, Addolorato G. Pharmacotherapy of acute alcoholic hepatitis in clinical practice. *World J Gastroenterol* 2014; **20**: 2159-2167 [PMID: 24605014 DOI: 10.3748/wjg.v20.i9.2159]

8 **Shi Y**, Zheng MH, Yang Y, Wei W, Yang Q, Hu A, Hu Y, Wu Y, Yan H. Increased delayed mortality in patients with acute-on-chronic liver failure who have prior decompensation. *J Gastroenterol Hepatol* 2015; **30**: 712-718 [PMID: 25250673 DOI: 10.1111/jgh.12787]

9 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1437.e1-e9 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

10 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, Fallon MB, Garcia-Tsao G, Maliakkal B, Malik R, Subramanian RM, Thacker LR, Kamath PS. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014; **60**: 250-256 [PMID: 24677131 DOI: 10.1002/hep.27077]

11 **Bañares R**, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, Saliba F, Sauerbruch T, Klammt S, Ockenga J, Pares A, Wendon J, Brünnler T, Kramer L, Mathurin P, de la Mata M, Gasbarrini A, Müllhaupt B, Wilmer A, Laleman W, Eefsen M, Sen S, Zipprich A, Tenorio T, Pavesi M, Schmidt HH, Mitzner S, Williams R, Arroyo V. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology* 2013; **57**: 1153-1162 [PMID: 23213075 DOI: 10.1002/hep.26185]

12 **Stadlbauer V**, Davies NA, Sen S, Jalan R. Artificial liver support systems in the management of complications of cirrhosis. *Semin Liver Dis* 2008; **28**: 96-109 [PMID: 18293280 DOI: 10.1055/s-2008-1040324]

13 **Kumar R**, Krishnamoorthy TL, Tan HK, Lui HF, Chow WC. Change in model for end-stage liver disease score at two weeks, as an indicator of mortality or liver transplantation at 60 days in acute-on-chronic liver failure. *Gastroenterol Rep* (Oxf) 2014; Epub ahead of print [PMID: 25391261 DOI: 10.1093/gastro/gou075]

14 **Starzl TE**, Van Thiel D, Tzakis AG, Iwatsuki S, Todo S, Marsh JW, Koneru B, Staschak S, Stieber A, Gordon RD. Orthotopic liver transplantation for alcoholic cirrhosis. *JAMA* 1988; **260**: 2542-2544 [PMID: 3050180 DOI: 10.1001/jama.1988.03410170090040]

15 **Weinrieb RM**, Van Horn DH, McLellan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. *Liver Transpl* 2000; **6**: 769-776 [PMID: 11084066 DOI: 10.1053/jlts.2000.18497]

16 **Prince MI**, Hudson M. Liver transplantation for chronic liver disease: advances and controversies in an era of organ shortages. *Postgrad Med J* 2002; **78**: 135-141 [PMID: 11884694 DOI: 10.1136/pmj.78.917.135]

17 **Bird GL**, O'Grady JG, Harvey FA, Calne RY, Williams R .Liver transplantation in patients with alcoholic cirrhosis: selection

criteria and rates of survival and relapse. *BMJ* 1990; **301**: 15-17 [DOI: 10.1136/bmj.301.6742.15]
18 **Pereira SP**, Howard LM, Muiesan P, Rela M, Heaton N, Williams R. Quality of life after liver transplantation for alcoholic liver disease. *Liver Transpl* 2000; **6**: 762-768 [PMID: 11084065 DOI: 10.1053/jlts.2000.19030]
19 **Schmeding M**, Heidenhain C, Neuhaus R, Neuhaus P, Neumann UP. Liver transplantation for alcohol-related cirrhosis: a single centre long-term clinical and histological follow-up. *Dig Dis Sci* 2011; **56**: 236-243 [PMID: 20499174 DOI: 10.1007/s10620-010-1281-7]
20 **Deruytter E**, Van Steenkiste C, Trépo E, Geerts A, Van Vlierberghe H, Berrevoet F, de Hemptinne B, Rogiers X, Troisi R, Colle I. Liver transplantation for alcoholic liver disease: a retrospective analysis of recidivism, survival and risk factors predisposing to alcohol relapse. *Acta Gastroenterol Belg* 2013; **76**: 282-290 [PMID: 24261021]
21 **Gutmann T**, Fateh-Moghadam B. Grundlagen einer gerechten Organverteilung. 8th ed. Berlin: Springer, 2003: 59-78
22 **Colak Y**, Tuncer I, Enc FY, Ozturk O, Kiziltas S, Ulasoglu C. Ecstasy induced fatal hepatic failure. *J Gastrointestin Liver Dis* 2011; **20**: 215-216 [PMID: 21725523]
23 **Mendizabal M**, Marciano S, Videla MG, Anders M, Zerega A, Balderramo DC, Chan D, Barrabino M, Gil O, Mastai R, Yantorno S, Gadano A, Silva MO. Changing etiologies and outcomes of acute liver failure: perspectives from 6 transplant centers in Argentina. *Liver Transpl* 2014; **20**: 483-489 [PMID: 24425668 DOI: 10.1002/lt.23823]
24 **Leong J**, Im GY. Evaluation and selection of the patient with alcoholic liver disease for liver transplant. *Clin Liver Dis* 2012; **16**: 851-863 [PMID: 23101986 DOI: 10.1016/j.cld.2012.08.012]
25 **Kranzler HR**, Armeli S, Wetherill R, Feinn R, Tennen H, Gelernter J, Covault J, Pond T. Self-efficacy mediates the effects of topiramate and GRIK1 genotype on drinking. *Addict Biol* 2014; Epub ahead of print [PMID: 25496338 DOI: 10.1111/adb.12207]
26 **Ferraguti G**, Pascale E, Lucarelli M. Alcohol addiction: a molecular biology perspective. *Curr Med Chem* 2015; **22**: 670-684 [PMID: 25544474]
27 **Burroughs AK**. Liver transplantation for severe alcoholic hepatitis saves lives. *J Hepatol* 2012; **57**: 451-452 [PMID: 22285999 DOI: 10.1016/j.jhep.2012.01.003]
28 **Ahn CS**, Hwang S, Kim KH, Moon DB, Ha TY, Song GW, Jung DH, Park GC, Kang SH, Jung BH, Kim N, Lee SG. Long-term outcome of living donor liver transplantation for patients with alcoholic liver disease. *Transplant Proc* 2014; **46**: 761-766 [PMID: 24767343 DOI: 10.1016/j.transproceed.2013.12.032]
29 **Anand AC**, Ferraz-Neto BH, Nightingale P, Mirza DF, White AC, McMaster P, Neuberger JM. Liver transplantation for alcoholic liver disease: evaluation of a selection protocol. *Hepatology* 1997; **25**: 1478-1484 [PMID: 9185771]
30 **Anantharaju A**, Van Thiel DH. Liver transplantation for alcoholic liver disease. *Alcohol Res Health* 2003; **27**: 257-268 [PMID: 15535454]
31 **Duvoux C**. [Liver transplantation: which indications? which results?]. *Presse Med* 2001; **30**: 711-716 [PMID: 11360736]
32 **Neuberger J**. Public and professional attitudes to transplanting alcoholic patients. *Liver Transpl* 2007; **13**: S65-S68 [PMID: 17969090 DOI: 10.1002/lt.21337]
33 **Kotlyar DS**, Burke A, Campbell MS, Weinrieb RM. A critical review of candidacy for orthotopic liver transplantation in alcoholic liver disease. *Am J Gastroenterol* 2008; **103**: 734-743; quiz 744 [PMID: 18081918 DOI: 10.1111/j.1572-0241.2007.01691]
34 **Sen S**, Felldin M, Steiner C, Larsson B, Gillett GT, Olausson M, Williams R, Jalan R. Albumin dialysis and Molecular Adsorbents Recirculating System (MARS) for acute Wilson's disease. *Liver Transpl* 2002; **8**: 962-967 [PMID: 12360442 DOI: 10.1053/jlts.2002.35546]
35 **Xu X**, Liu X, Ling Q, Wei Q, Liu Z, Xu X, Zhou L, Zhang M, Wu J, Huang J, Sheng J, Zheng S, Li L. Artificial liver support system combined with liver transplantation in the treatment of patients with acute-on-chronic liver failure. *PLoS One* 2013; **8**: e58738 [PMID: 23516546 DOI: 10.1371/journal.pone.0058738]
36 **Ling Q**, Xu X, Wei Q, Liu X, Guo H, Zhuang L, Chen J, Xia Q, Xie H, Wu J, Zheng S, Li L. Downgrading MELD improves the outcomes after liver transplantation in patients with acute-on-chronic hepatitis B liver failure. *PLoS One* 2012; **7**: e30322 [PMID: 22291934 DOI: 10.1371/journal.pone.0030322]
37 **Olson JC**, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, Kamath PS. Intensive care of the patient with cirrhosis. *Hepatology* 2011; **54**: 1864-1872 [PMID: 21898477 DOI: 10.1093/alcalc/agn013]
38 **Rice JP**, Lucey MR. Should length of sobriety be a major determinant in liver transplant selection? *Curr Opin Organ Transplant* 2013; **18**: 259-264 [PMID: 23492643 DOI: 10.1097/MOT.0b013e32835fb94b]
39 The Universal Declaration of Human rights. General Assembly resolution 217A. Available from: URL: http://www.un.org/en/documents/udhr/

P- Reviewer: Boin IFSF, Du C, Detry O, Dehghani SM, Fujino Y
S- Editor: Qi Y **L- Editor**: Rutherford A **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327