Hepat Mon. 2017 January; 17(1):e45788. doi: 10.5812/hepatmon.45788.

Published online 2017 January 22. **Editorial**

Generic Direct Acting Antiviral Treatment: The First Step Towards Elimination of Hepatitis C in Iran

Behzad Hajarizadeh[1,*]

[1]The Kirby Institute, UNSW Sydney (University of New South Wales), Sydney, Australia

[*]*Corresponding author*: Behzad Hajarizadeh, Viral Hepatitis Clinical Research Program, The Kirby Institute, UNSW Sydney, Wallace Wurth Building, NSW 2052, Australia. Tel: +61-293859208, Fax: +61-2938 0876, E-mail: bhajarizadeh@kirby.unsw.edu.au

Received 2017 January 17; **Accepted** 2017 January 21.

Keywords: Hepatitis C, Treatment, Generic, Direct Acting Antiviral, Elimination, Iran, Sofosbuvir, Daclatasvir, Cirrhosis

World health organisation (WHO) has released service coverage targets for viral hepatitis control, called as viral hepatitis elimination targets. For hepatitis C virus infection (HCV), the targets are to diagnose 90% and to treat 80% of people with chronic HCV infection by 2030 (1).

In Iran, the estimated prevalence of HCV exposure in general population is 0.39% (2). It is estimated that 186,500 individuals are living with chronic HCV infection in Iran, among whom 35% have been diagnosed and only 2.4% receive treatment annually (2).

The availability of highly effective, well tolerated, and easy-to-administer direct acting antiviral (DAA) regimens for HCV infection has resulted in a realistic optimism to reach ambitious WHO targets in many settings although high drug pricing is a major barrier to broadening the treatment access in the majority of the countries (3). Reduced prices can be obtained through manufacturing generic formulations of the drugs. Over the past decade, generic competition has resulted in a progressive price reduction of HIV antiretroviral therapy from US$ 10,000 to US$60 per patient per year which was a major enabler for expanding access to treatment in the resource-limited settings (4). Generic DAAs are manufactured in several countries such as Iran, Egypt, India, Pakistan, Bangladesh, China, Brazil and Morocco, either under the voluntary license agreement of the patent holder companies or using compulsory licensing (5, 6). While there are concerns about the sufficient oversight of generic manufacturing (6, 7), publicly available data of bioequivalence, clinical effectiveness and safety of the quality assured generic DAAs can encourage confidence in the quality of these drugs.

In this issue of Hepatitis Monthly, Merat et al. reported the data of effectiveness and safety of a generic fixed dose combination of sofosbuvir/daclatasvir, manufactured in Iran (8). This study is one of the few studies globally evaluating the clinical effectiveness of generic DAAs (9-11), among which it is the only study restricting the study population to cirrhotic patients. Among 100 recruited cirrhotic patients with genotype 1 or 3 (5 with decompensated cirrhosis and 4 post-liver transplantation), the overall sustained virologic response (SVR) was 92% by intention-to-treat analysis which was comparable to that from phase 3 clinical trials of the branded sofosbuvir plus daclatasvir in cirrhotic patients (12-14). Among those completed the study (n = 94), SVR was 98% in both groups of patients with genotype 1 (52/53) and genotype 3 (40/41). With respect to the drug safety, one patient experienced serious adverse event leading to treatment discontinuation and one patient died due to perforated duodenal ulcer and sepsis. Both patients had decompensated cirrhosis.

As the authors mentioned in their paper, the SVR reported in this study (92%) seems higher than that in ALLY-1 study (83%) of the branded drugs in cirrhotic patients of five genotypes (13). However, the 95% confidence intervals overlapped (87% - 97% vs. 71% - 92%, respectively) and there were also differences in the background characteristics of the participants in two studies, including the proportion of those with decompensated cirrhosis or Child-Pugh class C. Further studies with larger and more comparable study populations are needed to assess the hypothesis suggesting Iranian HCV patient responding better to DAA treatment.

This study demonstrated a high effectiveness of generic sofosbuvir/daclatasvir in genotype 1 and 3, the two most prevalent genotypes in Iranian people with HCV infection. However, there are still other key requirements as a foundation to achieve WHO targets to control HCV infection in Iran, including HCV care service price reform, enhanced HCV diagnosis and linkage to care, and high-coverage harm reduction (3).

Affordability is central to the HCV treatment uptake. The price of generic sofosbuvir/daclatasvir in Iran is about Rial 25,200,000 for four weeks (28 pills) which is equal to about US$ 630. For the patients having medical insur-

ance, the out-of-pocket cost decreases to Rial 7,560,000 (US$ 190). Although this cost is much lower than that for the branded drugs, the affordability of the drugs should be re-evaluated considering the economic status and purchasing power of the target population. People who inject drugs (PWID) are the main population at risk of HCV infection in Iran. They are mainly marginalised and in the lowest socio-economic status levels. Adding the cost of minimum-required pre-treatment and post-treatment laboratory tests, the total out-of-pocket cost of HCV care for a patient receiving 12 weeks generic sofosbuvir/daclatasvir will come to, Rial 28,500,000 (US$ 712) for those having medical insurance or Rial 87,800,000 (US$ 2,200) for those with no insurance which is far from being affordable for the vast majority of PWID.

An estimated 35% of Iranian people with HCV infection have been diagnosed (2) which is much lower than the WHO target (90% by 2030) (1). Moreover, a modelling study demonstrated that increasing in HCV diagnosis rate in addition to a treatment scale-up is needed to achieve at least 90% reduction in the number of people with HCV infection by 2030 (2). Simplified HCV diagnostic procedures, including dried blood spot testing and point-of-care testing, have been effective in increasing HCV diagnosis (15, 16).

The current model of HCV treatment delivery in Iran which relies on specialist care in the specialist clinics or hospitals will restrict treatment scale-up, particularly in remote areas. DAA therapy per se has a potential to boost the current capacity of specialist clinics, given the shortened treatment duration and simplified on-treatment monitoring. However, given the high tolerance and ease of delivery of DAA therapy, other strategies can further facilitate access to treatment, such as decentralization of service delivery through authorisation of trained general practitioners to prescribe DAA in the settings where access to specialist services is difficult or not cost-effective. For PWID, an integrated model of care through provision of HCV care in opioid substitution therapy (OST) clinics and using peer-support services to engage PWID in HCV care can increase treatment uptake (17, 18).

High-coverage harm reduction programs such as OST and needle and syringe programmes (NSP) are effective strategies for prevention of initial HCV infection and HCV re-infection after successful treatment. Moreover, these services can provide an access point for PWID, to engage in HCV education, testing, and potentially treatment.

In summary, Merat et al. study provided data of high effectiveness and safety of generic sofosbuvir/daclatasvir. Availability of safe and effective generic DAAs is a key step towards treatment scale-up although there are still other key challenges to be confronted to be able to achieve HCV control in the national level.

Footnote

Financial Disclosure: The Kirby Institute is funded by the Australian government department of health and is affiliated with the Faculty of Medicine, UNSW Sydney. The views expressed in this publication do not necessarily represent the position of the Australian government. The author is recipient of the national health and medical research council of Australia (NHMRC) early career fellowship.

References

1. World Health Organization . Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: World Health Organization; 2016.
2. Hajarizadeh B, Razavi-Shearer D, Merat S, Alavian SM, Malekzadeh R, Razavi H. Liver Disease Burden of Hepatitis C Virus Infection in Iran and the Potential Impact of Various Treatment Strategies on the Disease Burden. *Hepat Mon.* 2016;**16**(7):ee37234. doi: 10.5812/hepatmon.37234. [PubMed: 27642346].
3. Hajarizadeh B, Grebely J, Martinello M, Matthews GV, Lloyd AR, Dore GJ. Hepatitis C treatment as prevention: evidence, feasibility, and challenges. *Lancet Gastroenterol Hepatol.* 2016;**1**(4):317–27. doi: 10.1016/s2468-1253(16)30075-9.
4. Ford N, Singh K, Cooke GS, Mills EJ, von Schoen-Angerer T, Kamarulzaman A, et al. Expanding access to treatment for hepatitis C in resource-limited settings: lessons from HIV/AIDS. *Clin Infect Dis.* 2012;**54**(10):1465–72. doi: 10.1093/cid/cis227. [PubMed: 22431808].
5. Freeman JA, Hill A. The use of generic medications for hepatitis C. *Liver Int.* 2016;**36**(7):929–32. doi: 10.1111/liv.13157. [PubMed: 27306303].
6. Ravinetto R, De Weggheleire A, Dorlo TP, Francque S, Sokkab A, Pouget C, et al. Predictable threats to public health through delaying universal access to innovative medicines for hepatitis C: a pharmaceutical standpoint. *Trop Med Int Health.* 2016;**21**(12):1490–5. doi: 10.1111/tmi.12784. [PubMed: 27671365].
7. Sarpel D, Dieterich D. The use of generics to treat chronic hepatitis C: not quite ready for the big stage. *Liver Int.* 2016;**36**(7):933–5. doi: 10.1111/liv.13155. [PubMed: 27306304].
8. Merat S, Sharifi AH, Haj-Sheykholeslami A, Poustchi H, Fattahi B, Nateghi-Baygi A, et al. The Efficacy of 12 Weeks of Sofosbuvir, Daclatasvir, and Ribavirin in Treating Hepatitis C Patients with Cirrhosis, Genotypes 1 and 3. *Hepat Mon.* 2016;**17**(1):e44564. doi: 10.5812/hepatmon.44564.
9. Freeman JA, Sallie R, Kennedy A, Jeffreys G, Savage A, Hill AM. High Sustained Virological Response Rates using Legally Imported, Generic Direct Acting Antiviral Treatment for Hepatitis C. *Hepatology.* 2016;**63**(1 SUPP):444A.
10. Yakoot M, Abdo AM, Yousry A, Helmy S. Very rapid virologic response and early HCV response kinetics, as quick measures to compare efficacy and guide a personalized response-guided therapy. *Drug Des Devel Ther.* 2016;**10**:2659–67. doi: 10.2147/DDDT.S111496. [PubMed: 27601883].
11. Hill AM, Golovin S, Dragunova J, Korologou-Linden RS. Virological Response rates using Generic Direct Acting Antiviral Treatment for Hepatitis C, Legally Imported into Russia. *Hepatology.* 2016;**63**(1 SUPP):1005A.
12. Ji D, Chen GF, Wang C, Wang YD, Shao Q, Li B, et al. Twelve-week ribavirin-free direct-acting antivirals for treatment-experienced Chinese with HCV genotype 1b infection including cirrhotic patients. *Hepatol Int.* 2016;**10**(5):789–98. doi: 10.1007/s12072-016-9755-0. [PubMed: 27443347].

13. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology.* 2016;**63**(5):1493–505. doi: 10.1002/hep.28446. [PubMed: 26754432].
14. Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology.* 2016;**63**(5):1430–41. doi: 10.1002/hep.28473. [PubMed: 26822022].
15. Sahajian F, Bailly F, Vanhems P, Fantino B, Vannier-Nitenberg C, Fabry J, et al. A randomized trial of viral hepatitis prevention among underprivileged people in the Lyon area of France. *J Public Health (Oxf).* 2011;**33**(2):182–92. doi: 10.1093/pubmed/fdq071. [PubMed: 20876189].
16. Hickman M, McDonald T, Judd A, Nichols T, Hope V, Skidmore S, et al. Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. *J Viral Hepat.* 2008;**15**(4):250–4. doi: 10.1111/j.1365-2893.2007.00937.x. [PubMed: 18086182].
17. Grebely J, Alavi M, Micallef M, Dunlop AJ, Balcomb AC, Phung N, et al. Treatment for hepatitis C virus infection among people who inject drugs attending opioid substitution treatment and community health clinics: the ETHOS Study. *Addiction.* 2016;**111**(2):311–9. doi: 10.1111/add.13197. [PubMed: 26451534].
18. Grebely J, Knight E, Genoway KA, Viljoen M, Khara M, Elliott D, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. *Eur J Gastroenterol Hepatol.* 2010;**22**(3):270–7. doi: 10.1097/MEG.0b013e32832a8c4c.