Enferm Infecc Microbiol Clin. 2020;38(2):94–95

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Letters to the Editor

Confirmation of antibodies against hepatitis C virus by recombinant immunoblot: Is it really an improvement to abandon it?

Confirmación de anticuerpos frente al virus de la hepatitis C mediante inmunoblot recombinante: ¿es realmente una mejora abandonarlo?

Dear Editor,

In 2013, following discontinuation of the FDA-approved recombinant immunoblot assay (RIBA), the USA Centers for Disease Control (CDC) updated their HCV testing algorithm with the withdrawal of the RIBA as supplemental test for anti-HCV and the recommendation of using only nucleic acid amplification test (NAAT), following anti-HCV screening reactive result. Results of a meta-analysis published in 2017, showed that the specificity of the methods in use for screening of antibodies against hepatitis C virus (anti-HCV) was excellent,[1] accordingly, the 2017 World Health Organization (WHO) recommendations also suggested to perform NAAT for chronic HCV confirmation following a reactive HCV serological test,[2] excluding again RIBA from recommendations. Accordingly, recommendations recently published in this journal by a group of experts from several Spanish hospitals parallel WHO and CDC guidelines.[3]

There are several points to consider regarding these recommended guidelines:

Among most recent studies, the results of a study in Egypt in 2016,[4] indicate the necessity of confirmation by RIBA in a country with a high prevalence of HCV infection because false positive screening results can occur quite frequently (28.6% in health care workers). On the other hand, a study carried out in a low HCV prevalence setting, published in 2017 by the Division of Viral Hepatitis National Center for HIV, Hepatitis, STD, and TB Prevention, at CDC,[5] also indicates a high frequency of false-positive anti-HCV screening results (a false positive rate up to 22% was observed) stating that "*screening persons in a population with low prevalence of a disease leads to many false-positives that may have health, economic and psychological impacts on patients and providers*".[5] Then, despite high specificity performance of the tests, the occurrence of false positive screening results seems to be significant (up 20%) both in areas of high and low prevalence of HCV infection.

The decision to exclude confirmation by RIBA from diagnostic algorithms is partially based on the assumption that a test detecting viremia following a reactive result on an anti-HCV screening test will effectively discard false positive results. This assumption should be nuanced: Firstly, although NAAT testing will indirectly confirm a screening reactive result only in case it is positive, absence of viremia does not exclude the true presence of anti-HCV. Secondly, NAAT testing will not identify in any case patients who have contacted the virus in the past but successfully resolved the acute infection. With the withdrawal of supplemental test for anti-HCV, it became challenging to discriminate false-positive results from resolved HCV infection. The approach of performing NAAT on screening reactive samples, will indeed correctly identify acute or chronic infections, however, it will not correctly identify the true HCV status of all other persons. These persons will consequently receive very imprecise information about their real HCV status. It is not surprising, therefore, that three quarters of the Spanish hospitals surveyed by the authors of the revision cited above declare they still perform RIBA tests to confirm the reactive samples in the screening.[3]

Accurate interpretation of anti-HCV-reactive results and a clear distinction between past, resolved HCV infection and a false-positive results is needed because of several aspects. First, a false positive result may have significant consequences for the patient in terms of time and cost. Second, if previous contact with HCV is confirmed, the patient would require prevention advice and continuous monitoring since reinfection could occur. Third, in a quality health care system, it seems a legitimate demand from all patients to receive information of equal quality on the results obtained with laboratory diagnostic tests that have been prescribed and performed. Fourth, individuals with a false-positive anti-HCV result would be incorrectly banned from donating blood, having a psychological impact on these persons and an impact on the available blood supply. Finally, in the Public Health field, abandoning correct information on the true HCV status would be unacceptable, since this would generate prevalence data quite far from reality due to the false positive results, which are still frequent.

In conclusion, we cannot agree with the recommendation to exclude the confirmation of anti-HCV by RIBA tests from the diagnostic test algorithm for HCV infection. We strongly encourage test centers to continue confirmatory testing in order to preserve the excellent quality of care provided to their patients.

DOI of original article: https://doi.org/10.1016/j.eimc.2018.05.016

References

1. Tang W, Chen W, Amini A, et al. Diagnostic accuracy of tests to detect hepatitis C antibody: meta-analysis and review of the literature. BMC Infect Dis. 2017;17 Suppl. 1:695–713.
2. World Health Organization. Guidelines on Hepatitis B and C testing; 2017. ISBN 978-92-4-154998-1.
3. Crespo J, Lázaro de Mercado P, Blasco AJ, et al. El diagnóstico de la infección por el virus de la hepatitis C en España: una oportunidad para mejorar. Enferm Infecc Microbiol Clín. 2019;37:231–8.
4. Rafik M, Bakr S, Soliman D, et al. Characterization of differential antibody production against hepatitis C virus in different HCV infection status. Virol J. 2016;13:116–23.
5. Moorman AC, Drobenuic J, Kamili S. Prevalence of false-positive hepatitis C antibody results National Health and Nutrition Examination Study (NHANES) 2007–2012. J Clin Virol. 2017;89:1–4.

Ana Avellón Calvo [a,*], José Manuel Echevarría Mayo [b]

[a] *Laboratorio de Referencia e Investigación en Hepatitis Víricas, Unidad de Hepatitis, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain*
[b] *Facultad de Biología, Universidad Complutense de Madrid, Spain*

* Corresponding author.
E-mail address: aavellon@isciii.es (A. Avellón Calvo).

https://doi.org/10.1016/j.eimc.2019.05.008
0213-005X/

In reply to: Confirmation of antibodies against hepatitis C virus by recombinant immunoblot: Is it really an improvement to abandon it?

En respuesta a: Confirmación de anticuerpos frente al virus de la hepatitis C mediante inmunoblot recombinante: ¿es realmente una mejora abandonarlo?

Dear Editor,

In spite of the high efficacy of antiviral treatment, for the first time in infectious diseases and in the absence of a vaccine, there is an opportunity to eliminate an infection, namely hepatitis C. WHO sets year 2030 as the target for HCV elimination,[1] and Spain is estimated to achieve WHO goals for elimination by 2024.[2] One of the barriers to elimination is appropriate screening: as EASL guidelines[3] state, "most laboratories use a two-step approach (phlebotomy and antibody test in step 1, and phlebotomy and a test for HCV RNA in step 2), resulting in a substantial fraction of patients with anti-HCV antibodies never receive confirmatory HCV RNA testing". For this reason both EASL and AASLD[4] guidelines, currently recommend that "if anti-HCV antibodies are detected, the presence of HCV RNA in serum or plasma should be determined to identify patients with ongoing infection (A1)". In addition, EASL guidelines recommend "Reflex testing for HCV RNA in patients found to be anti-HCV antibody-positive should be applied to increase linkage to care (B1)". Several Spanish studies have already reported the benefits of reflex testing on linkage to care[5,6] and on health economics.[7] Reflex testing is supported by all Spanish scientific societies involved in HCV care.[8]

We believe that the reasons for continuing supplementary antibody confirmation testing proposed by Avellón et al. may be out of scope for clinical management and may hamper the elimination goals of hepatitis C. First, a 20% of false positive tests is not acceptable for any screening test in the clinical laboratory, and is far beyond the specificity of 3rd and 4th generation FDA cleared and CE marked immunoassays to detect anti-HCV. Second, the statement "*the decision to exclude confirmation by RIBA from diagnostic algorithms is partially based on the assumption that a test detecting viremia following a reactive result on an anti-HCV screening test will effectively discard false positive results*" is misleading. Reflex testing is not intended to discard any false positive result of anti-HCV; it is intended to diagnose active infection by HCV and to identify and link to care those patients that need and may benefit from treatment. This is the clinical need for clinicians, and is the need to achieve elimination goals. With reflex testing patients, and clinicians, will receive the clinical information they really need, it is not a case of reporting false or true positive results on HCV antibodies. The only room for discrimination between false positive results and cleared HCV infections is clinical and epidemiological research. There is no need of it in clinical practice and with elimination purposes. In our opinion, it is unclear how "*false positive result may have significant consequences for the patient in terms of time and cost*", nor "*if previous contact with HCV is confirmed, the patient would require prevention advice and continuous monitoring since reinfection could occur*", as this is already recommended by clinical guidelines with annual HCV-RNA testing for all patients with ongoing risk factors for HCV acquisition. Dr. Avellon states that "*legitimate demand from all patients to receive information of equal quality on the results obtained with laboratory diagnostic tests that have been prescribed and performed*". However, we believe that the demand of the patient is to be cured, and the goal for Public Health System is to achieve the elimination of hepatitis C, rather than start a debate on if prevalence data are or not "*quite far from reality due to the false positive results*".

In conclusion, there is sufficient data to support that using supplementary methods for the confirmation of anti-HCV antibodies should be abandoned in clinical practice in the Spanish network of diagnostic laboratories, as it results in a barrier for appropriate clinical management and for linkage to care, and hampers HCV elimination in Spain.

References

1. World Health Organization (WHO). Draft global health sector strategies. Viral hepatitis, 2016–2021. Global health sector strategy on viral hepatitis 2016–2021. 2016.t. WHO; 2016. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-EN?ua=1
2. Razavi H, Gonzalez YS, Pangerl A, Cornberg M. Global timing of hepatitis C virus elimination: estimating the year countries will achieve the World Health Organization elimination targets. In: EASL 2019. 2019.
3. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69:461–511.
4. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org [accessed July 2018].
5. Casas P, Navarro D, Aguilera A, García F. A pilot study on the implementation of reflex testing for the diagnosis of active hepatitis C virus infection. Enferm Infecc Microbiol Clin. 2019;37:348–9.
6. De La Paz Casas Hidalgo M, Viciana I, Montiel N, De La Iglesia A, Domínguez A, Freyre-Carrillo C, et al. Implementación de la estrategia del diagnóstico en un sólo paso de la infección activa por Virus de la Hepatitis C en Andalucía. Enferm Infecc Microbiol Clin. 2018;36(Espec Cong):3.
7. García F, Domínguez-Hernández R, Alados JC, Casado M, Macías J, Téllez F, et al. La simplificación del proceso de diagnóstico de la hepatitis C crónica es una estrategia coste-efectiva. Enferm Infecc Microbiol Clin. 2019;37:634–41.
8. Diagnóstico de la hepatitis C en un solo paso. Asociación Española para el Estudio del Hígado. Available from: http://aeeh.es/wpcontent/uploads/2016/01/DX1P-AEEH-AEHVE-SEIMC-SEPD-definitivo.pdf [Internet].

Federico García [a,b,*], Antonio Aguilera [b,c], Javier Crespo [d], Juan A. Pineda [b,e]

[a] *Servicio de Microbiología, Hospital Universitario San Cecilio, Instituto de Investigación Biosanitaria Ibs.GRANADA, Granada, Spain*
[b] *Grupo de Estudio de Hepatitis Virales GEHEP-SEIMC*
[c] *Servicio de Microbiología, Complexo Hospitalario Universitario de Santiago, Instituto de Investigación Sanitaria de Santiago IDIS, Santiago de Compostela, Spain*
[d] *Servicio Aparato Digestivo, Hospital Universitario Marqués de Valdecilla, IDIVAL, UNICAN, Santander, Spain*
[e] *Unidad de Enfermedades Infecciosas, Hospital Universitario de Valme, Sevilla, Spain*

* Corresponding author.
E-mail address: fegarcia@ugr.es (F. García).

https://doi.org/10.1016/j.eimc.2019.07.001
0213-005X/