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Commentary

Immunization recommendations against hepatitis A in Spain: Effectiveness of immunization in MSM and selection of antigenic variants

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Most countries of the European Union/European Economic Area (EU/EEA) present low or very low endemicity regarding hepatitis A, and this can be the reason why the vaccine against hepatitis A virus (HAV) is not included as a systematic vaccine in the National Immunization Programme and is only recommended for risk groups. In this context, most of the young population in Western Europe is susceptible to HAV [1] and the transmission of infection by certain sexual practices has gained great importance, as has been shown in several outbreaks in the group of men who have sex with men (MSM) [2].

Vaccination recommendations in the EU/EEA are not homogeneous. Most countries follow the WHO recommendations that advise the immunization of risk groups, which have higher probability of infection or worse prognosis after infection, although a high level of heterogeneity in the definition and selection of risk groups is found among the different countries. Immunization of MSM is recommended in many countries but very few include also HIV-infected persons [3].

In recent years, restrictions and prioritization on the use of vaccines against HAV were established in several countries due to shortage of these vaccines worldwide. In the case of Spain, the administration of only one dose of this vaccine was recommended in the main risk groups, and assessing the administration of the second dose after the reestablishment of the supply, except in the case of immunosuppressed persons in whom the complete scheme of two doses was recommended. Priority was given to the immunization of MSM due to the outbreak going on in Spain and other EU countries.

In an article recently published in *EBioMedicine* [4], it was warned that reducing the amount of antigen or the number of doses against HAV in MSM could have implications in the evolution of the virus and in the potential emergence of variants that can escape the protection of the vaccine. In that study, the evolution of the HAV was analysed in five cases of hepatitis A in vaccinated MSM, comparing with eight unvaccinated hepatitis A patients. A positive selection of antigenic variants in some vaccinated patients compared with the unvaccinated was suggested and concerns raised to the new vaccination policies directed to the MSM [4].

We would like to point out some considerations regarding the specific vaccinated cases described in the article as well as to summarize the current immunization policy in Spain. Concerning these cases studied and classified as vaccine failures, we would like to highlight that none of them had been correctly vaccinated according to the vaccination criteria established in Spain. The first one, a 34-year-old non-HIV-infected patient, had been vaccinated in childhood with an incomplete regimen (2 doses of Twinrix® paediatric; the appropriate schedule is three doses). The second patient, an immunocompetent HIV-infected patient, had also received an incomplete vaccination scheme 2 years earlier (2 doses of Twinrix® for adults). The third and fourth had received a single adult dose of Twinrix® and both were immunocompetent HIV-infected patients. Finally, the fifth patient, aged 34 and not infected with HIV, had received an incomplete regimen (2 adult doses of Twinrix®) during the incubation period. Although immunocompetent, three of them were HIV-infected patients.

We would also like to highlight that development of immunity occurs in about 83% of HIV-infected patients when they have a good immunologic status [5]. Additionally, we should consider the possibility of early loss of seroresponse (also known as seroreversion) after an adequate response to vaccination [6]. For these reasons, it is recommended to make serological markers after vaccination in HIV-infected persons.

Current vaccination policy in Spain, recommend immunization with monovalent hepatitis A vaccine in HIV-infected persons, with the following regimen: two doses separate at least 6 months if CD4 is higher than 350 cells/μl and 3 doses at 0, 1 and 6 months for those with CD4 lower than 350 cells/μl. In both situations the response to the vaccine should be checked by serological markers 2–3 months after receiving the last dose, and in case of no seroresponse an additional dose of vaccine should be administered [7]. In MSM not infected with HIV, and without other comorbidity, vaccination against HAV is recommended with two doses at 0 and 6 months. If hepatitis B vaccine is also recommended, a vaccine including both antigens against hepatitis A and hepatitis B can be administered with a three-dose regimen (0, 1 and 6 months). Sexual behaviour, although increasing the risk of HIV infection, does not cause immunosuppression on its own [8], and therefore the administration of a single dose to immunocompetent people is

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correct in situations of shortage as the one that forced restrictions in vaccination in 2017.

The inactivated vaccine against HAV is extraordinarily immunogenic producing seroconversion in almost 100% of people a month after the administration of a single dose [9], demonstrating maintenance of protective antibody titres for at least 11 years and inducing immunologic memory. The administration of a single dose of vaccine was observed to produce a specific cellular response similar to the one produced by natural infection or after a second dose of vaccine. In addition, the specific T-cell immunity against HAV induced by primary vaccination is maintained regardless of the protective level of plasma antibodies [10].

The limitations of vaccination against hepatitis A to provide protection to immunosuppressed patients are due to the peculiarities of the patients and not to the characteristics of the vaccine. The best strategy to avoid the HAV infection in these patients is to increase the protection of the population that can be the source of the virus, that is, increasing coverage in risk groups.

Disclosure

The authors have nothing to disclose.

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