1. Study name

1.1 Study name: Vaccination adjuvated against hepatitis B in Spanish National Healthcare System (SNS) workers typed as non-responders to conventional vaccines

1.2 Protocol number: IBS-VACANTIB-1701

1.3 EU Trial number: ClinicalTrials.gov Identifier: NCT03410953

1.4 Other identifiers: EudraCT-number 2016-004991-23

1.5 Abstract

Trial Design: An interventional, phase 4, single group assignment, without masking (open label), preventive clinical trial was carried out in health workers with biological risk in their tasks, who have been filed as non-responders to conventional vaccination against Hepatitis B.

Methods: 67 health workers with biological risk in their tasks, who have been filed as non-responders to conventional vaccination against Hepatitis B, were enrolled in the Clinical Trial. All participants were from 18 years up to 64 years old. Inclusion Criteria: NHS workers -including university students doing their internships in health centres dependent on the National Health System (inclusion of students is regulated and limited by specific instructions on labour prevention in each autonomous community)- classified as non-responders. The criteria defining them as non-responders to the conventional hepatitis B vaccine is anti HBsAb titers < 10 mUI/ml following the application of six doses of conventional vaccine at 20 lg doses (two complete guidelines). The objective of this study was to provide Health workersstaff with an additional protection tool against hepatitis B infection, and to evaluate the efficacy of the adjuvanted vaccine in healthy non-responders to conventional hepatitis B vaccine. The primary outcome was the measurement of antibody antiHBs before the first Fendrix® dose and a month after the administration of each dose. Other outcome was collection of adverse effects during administration and all those that could be related to the vaccine and that occur within 30 days after each dose. In this study, only one group was assigned. There was no randomization or masking.

Results: The participants were recruited between April 13, 2018 and October 31, 2019. 67 participants were enrolled in the Clinical Trial and included the analyses. The primary immunisation consists of 4 separate 0.5 ml doses of Fendrix®, administered at the following schedule: 1 month, 2 months and 6 months from the date of the first dose. Once the positivity was reached in any of the doses, the participant finished the study and was not given the following doses. 68.66% (46 out 67) had a positive response to first dose of Fendrix®. 57.14% (12 out 21) had a positive response to second dose of Fendrix®. 22.22% (2 out 9) had a positive response to third dose of Fendrix® and 42.96% (3 out 7) had a positive response to last dose of Fendrix®. Overall, 94.02% (64 out 67) of participants had a positive response to Fendrix®. No serious adverse event occurred.

Conclusions: The use of Fendrix®, is a viable vaccine alternative for NHS workers classified as ‘‘nonresponders”. Revaccination of healthy non-responders with Fendrix®, resulted in very high proportions of responders without adverse events.

Trial registration: The trial was registered in the Spanish National Trial Register (REEC), ClinicalTrials.gov and inclusion has been stopped (identifier NCT03410953; EudraCT-number 2016- 004991-23).

Funding: GRS 1360/A/16: Call for aid for the financing of research projects in biomedicine, health management and socio-health care to be developed in the centres of the Regional Health Management of Autonomous Community of Castile-Leon. In addition, this work has been supported by the Spanish Platform for Clinical Research and Clinical Trials, SCReN (Spanish Clinical Research Network), funded by the Subdirectorate General for Research Evaluation and Promotion of the Carlos III Health Institute (ISCIII), through the project PT13/0002/0039 and project PT17/0017/0023 integrated in the State Plan for R&D&I 2013–2016 and co-financed by and the European Regional Development Fund (ERDF).

2. Who sponsored this study?

Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León- Instituto de Investigación Biomédica de Salamanca (IBSAL)

3. General information about the clinical trial

3.1 Where was the study done?

Eleven SNS hospitals participated in this clinical trial, and these are listed below:

- Complejo Asistencial Universitario de Salamanca. (Coordinating Center)
- Hospital Clínico Universitario de Valladolid
- Complejo Asistencial de Zamora
- Complejo Asistencial Universitario de León
- Complejo Asistencial Universitario de Palencia
- Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid.
- Hospital Clínico San Carlos, Madrid.
- Hospital Universitario 12 de Octubre, Madrid.
- Hospital Universitario Gregorio Marañón, Madrid.
- Hospital Universitario Puerta de Hierro, Madrid.
- Hospital Universitario Ramón y Cajal, Madrid.

3.2 When was this study done?

Dates that define the periods of recruitment and follow-up. From 26 April 2018, the date of the inclusion of the first subject, to 11 June 2019, the date of the inclusion of the last subject, 94 individuals were assessed for eligibility, of whom 67 were included in the present study (Fig. 1). Follow-up continued until 31 October 2019. On 14 November 2019, the trial was concluded with 67 recruited subjects. Of the 94 subjects assessed for eligibility, 27 did not agree to participate in the trial and declined to sign an informed consent form. In the absence of losses or exclusions, data analysis was conducted with 67 subjects.

3.3 What was the main objective of this study?

Objectives

- To endow Spanish Health Service staff with additional protection against hepatitis B infection.
- To assess the efficacy of the adjuvanted vaccine in healthy subjects who do not respond to the conventional hepatitis B vaccine.

Hypothesis

- Administration of the Fendrix® vaccine is a viable alternative for Spanish Health Service staff classified as ‘‘non-responders”.

4. What patients/people were included in this study?

4.1 the number of subjects included in the trial by country both within and outside af the EU

The vaccine was only administered to subjects whose previous serology was negative. Thus, the first dose was administered to 67 subjects, the second dose to 21 subjects, the third to 9 subjects and the fourth to 7 subjects.

4.2 Age group and gender breakdown

18 Years to 64 Years (Adult)

4.3 Inclusion and exclusion criteria

In order to be recruited for this clinical trial, subjects had to work in the SNS —including university students undertaking work placements in SNS health centres (subject to and limited by the specific regulations on health and safety in each autonomous region)— and be of working age. In addition, they had to be free of any condition that contraindicated vaccination with Fendrix®. They also had to meet the criteria for classification as a non-responder to the conventional hepatitis B vaccine: anti-HBs antibody titers of <10 mIU/ml following administration of six 20 µg doses of conventional vaccine (two complete series). All subjects signed an informed consent form.

The exclusion criteria were as follows: known allergy to the active ingredient or to any other of the drug components (included in section 6 of the summary of product characteristics); a past allergic reaction to any hepatitis B vaccine; or presenting a serious infection with fever at the time of recruitment. Subjects who did not give their informed consent were also excluded.

5. Which medicines (or vaccines) were studied?

Fendrix®, the hepatitis B vaccine formulated with the new AS04 adjuvant (MPL + aluminum salts) by GlaxoSmithKline.

6. What were the side effects?

The 67 participants reported 32 adverse effects (AEs), of which 25 were adverse reaction (AR). None of the adverse effects reported were considered serious and all patients recovered from their corresponding adverse effect, suggesting a low risk of serious adverse effects and an acceptable risk in relation to non-serious adverse effects, which corresponded to those already identified in the Technical Data Sheet.

Four subjects had diabetes mellitus type 2 prior to participating in the trial. Van Der Meeren et al reported that the reactogenicity and safety profile of the hepatitis B vaccine (Engerix- BTM) appeared similar in controls and patients with hepatitis B and was consistent with the experience of the vaccine). Two of them did not reach a response after 4 doses of Fendrix® and the others attained seroprotection after the fourth dose. Another non-responder had autoimmune hepatitis prior to participating in the trial and the last non-responder did not present any pathologies of interest.

Risk-benefit assessment. An analysis of the results revealed no evidence of significant, identifiable or potential risks related to administration of Fendrix in the study population (health service staff and university students whose work in the SNS exposed them to biological risk and who had been classified as nonresponders to the hepatitis B vaccine), beyond those already indicated in the Technical Data Sheet.

7. What were the overall results of the study?

Results and estimation

Of the 67 subjects participating in this trial, 63 (94.03%) attained anti-HBs levels of ≥10 mIU/ml, indicating seroprotection against HBV. A cumulative analysis of the response data indicated a gradual increase in subjects reaching seroprotection: 68.66% with the first dose, 86.57% with the second dose, 89.55% with the third dose and 94.03% with the fourth dose. We did not detect any serious adverse effects during this clinical trial. Most of the adverse effects observed occurred after administering the first dose. Some 30% of vaccinations (32 out of 104) gave rise to adverse effects, and of these, 78.12% were related to the medication under study. The symptoms were transient and almost all resolved spontaneously within 1 week. By symptom, the most common effect (59.38%) was pain at the injection site. Seven adverse effects were not associated with the medication, and the most common of these was ‘‘malaise”.

Secondary analysis

- We found a relationship between sex and response to the first vaccine dose.
- We also analyzed the influence of age on vaccine response and observed a significant correlation between age and response to the first dose. This finding indicates an inverse correlation between variables, whereby the higher the age, the lower the response.
- The adverse effects reported following administration of the first dose appear to be linked to not attaining seroprotection.
- We do not see any relationship between the time between previous vaccination and vaccination with Fendrix® and the response to Fendrix®.

8. How has this study helped patients and re searchers?

From the perspective of health, Fendrix® represents a viable alternative vaccine for SNS staff classified as ‘‘non-responders”. As regards costs, according to previous publications, the ‘‘cost” of the vaccine is offset by savings in:

- The cost of follow-up after a biological accident.
- The cost of administering specific immunoglobulin.
- The personal cost to the worker concerned.
- The level of response to a single dose.

Extrapolation. The off-label use of Fendrix® described here will enable its administration to many potential beneficiaries if the AEMPS approves such off-label use. These include:

- Health service staff
- Non-health service staff
- Employees in workplaces related to health care
- State security forces
- Prison officers

9. Are there plans for further studies?

Our results pave the way for replicating the trial in other countries.

10. Where can I find more information about this study?

The data and results of this clinical trial have been published in the journal Vaccine, Volume 39, Issue 3, 15 January 2021, Pages 554-563:

https://doi.org/10.1016/j.vaccine.2020.12.006

Protocol: For protocol see https://clinicaltrials.gov/ct2/show/NCT03410953