A comparison of two Fendrix hepatitis B vaccination schedules in patients with inflammatory bowel disease

Kuiper, V.P.; Plas, P. van der; Hoogerwerf, M.A.; Koopman, J.P.R.; Meulen, A.E. van der; Roukens, A.H.E.; ... ; Roestenberg, M.

Vaccine 40 (2022) 6201–6205

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

A comparison of two Fendrix hepatitis B vaccination schedules in patients with inflammatory bowel disease

Vincent P. Kuiper [a], Pauline van der Plas [b], Marie-Astrid Hoogerwerf [a], Jan Pieter R. Koopman [b], Andrea E. van der Meulen [c], Anna H.E. Roukens [a], Leo G. Visser [a], Meta Roestenberg [a,b,*]

[a] Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands
[c] Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 6 October 2021
Received in revised form 31 August 2022
Accepted 2 September 2022
Available online 22 September 2022

Keywords:
Inflammatory bowel disease
Hepatitis B
Vaccination
Fendrix

ABSTRACT

Systemic immunosuppressive therapy (IS) renders patients with inflammatory bowel disease (IBD) vulnerable to fulminant hepatitis B virus (HBV) infection. Seroprotection against HBV through a full vaccination scheme is preferably obtained before IS is initiated, but often conflicts with the clinical need to initiate therapy rapidly. Consequently, the vast majority of patients will use IS during booster vaccinations. In this retrospective cohort study, we examined the serological response after a modified vaccination schedule which includes an initial double dose of Fendrix in patients with IBD and compared the results with the serological responses of patients with IBD who received the standard schedule. Seroprotection rates were 86.2 % and 88.9 % in the modified and standard schedule groups respectively. One-third of patients obtained seroprotection after only one double dose vaccine. A double dose may be considered in patients with IBD at high short-term risk of HBV infection when a rapid protective response is warranted.

1. Introduction

In countries where HBV is endemic, patients with inflammatory bowel disease (IBD) are at increased risk of hepatitis B virus (HBV) infection [1,2]. Moreover, the increased use of systemic immunosuppressive therapy renders patients with IBD vulnerable to fulminant infections and reactivation of chronic HBV infection with potentially fatal outcomes [3]. As such, the consensus among experts is to recommend screening for HBV in all patients at diagnosis of IBD and to vaccinate all who are seronegative [4]. Serological responses to HBV vaccine in immunocompromised patients, including those that have IBD treated with immunosuppressive medication, are suboptimal with observed seroprotection rates of 61 %; considerably lower than the > 90 % seroprotection rates in healthy individuals [5], mainly due to interference of immunosuppressive medication with vaccine responsiveness. The most widely used schedule for hepatitis B vaccination is Engerix-B doses given at timepoints 0, 1 and 6 months, but to increase vaccine efficacy, different HBV vaccination schedules or novel adjuvanted vaccines in patients with IBD are being considered [4,6,7].

Fendrix is a novel HBV vaccine registered for patients with chronic kidney diseases, which contains GlaxoSmithKline's proprietary AS04C adjuvant, a toll-like receptor 4 agonist. Through increased immunogenicity of the antigen with the adjuvant, this vaccine may also be beneficial to immunocompromised patients. Indeed, revaccination with Fendrix of patients with HIV that were nonresponding to other HBV vaccines resulted in high success rates [8,9]. Recently, Fendrix was shown to induce higher seroprotective anti-HBs titers in patients with IBD, comparable with double doses of Engerix-B [7].

In our tertiary center hospital, we vaccinate all newly diagnosed patients with IBD that are HBV seronegative with Fendrix at timepoints 0, 1 and 6 months. Whereas the first vaccination is often given before initiating immune suppressive therapy, we found that at the time of the second and third dose the vast majority of these patients have initiated systemic immune suppressive therapy. To overcome diminished vaccine responses due to these therapies, we modified the vaccination schedule to provide the first two doses at the same time (initial double dose) as to prime these patients with higher antigen doses. In this retrospective study, we have evaluated the serological responses of the modified schedule and compared them with the standard schedule.

* Corresponding author at: Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands.
E-mail address: m.roestenberg@lumc.nl (M. Roestenberg).

https://doi.org/10.1016/j.vaccine.2022.09.006
0264-410X/

2. Methods

2.1. Study participants and vaccination schedules

This retrospective single center cohort study was conducted at the Leiden University Medical Center, department of Infectious Diseases, Leiden, The Netherlands. We assessed data from adult patients with IBD who were referred to the Infectious Diseases specialist for immunization counseling in anticipation of initiation or change of systemic immunosuppressive therapy. Two HBV vaccination schedules were assessed: a modified schedule and a standard schedule.

In 2016 and 2017, spanning a period of 22 months, all patients with IBD that required HBV vaccinations were vaccinated with a double dose of Fendrix at time of diagnosis, before initiation of immunosuppressive therapy (per dose: 0.5 ml, 20 μg of recombinant HBsAg adjuvanted by 50 μg of AS04C; GlaxoSmithKline), this group is referred to as the modified schedule group. The rationale was to induce a quick and early response to vaccination before systemic immunosuppression would be administered. Anti-HBs antibody titers were assessed four weeks after a double dose vaccination. Patients with anti-HBs titers $\geq$ 10 IU/L were considered seroprotected and were not administered subsequent doses. Patients that did not reach seroprotection received additional vaccinations with single doses of Fendrix until seroprotection was reached or until they were considered non-responding. The timing of subsequent vaccinations was > 4 weeks and aligned with the patients visits to the gastroenterologist. Moreover, subsequent vaccinations were preferably not administered during the course of increased immunosuppression such as during induction therapy with systemic immunosuppressives. Generally, up to three vaccinations were given to reach seroprotection, however any subsequent vaccinations were given at the discretion of the treating physician. Serological status was assessed after each vaccination.

As a comparison group, patients with IBD that received the standard of care (referred to as the standard schedule group), i.e. single Fendrix doses at 0, 1 and 6 months, were included from 2015 (before the modified schedule was implemented) and up to 2018. Patients were included until the same groups size as the modified schedule group was obtained. The standard schedule included an anti-HBs titer measurement four weeks after the second vaccination, and after any subsequent vaccinations if seroprotection was not reached following the first two vaccinations. Any additional vaccinations given (more than was intended in the 0, 1 and 6 months schedule) was at the discretion of the treating physician.

All included patients had negative anti-HBs titers before vaccination and none were previously vaccinated against hepatitis B.

2.2. Outcomes

The primary endpoint was the seroprotection rate after completion of the vaccination schedule. Additionally, seroprotection rates at intermediate timepoints were assessed. In addition, anti-HBs geometric mean titers (GMT) were compared at the final timepoint. As an exploratory endpoint, clinical factors that were predictive of early response, i.e. reaching seroprotection after the first double dose of Fendrix, were evaluated.

2.3. Definitions

Seroprotection was defined as having an anti-HBs $\geq$ 10 IU/L.

Exposure to systemic immunosuppressive therapy was categorized as follows:

1. No medication: patient was not receiving any systemic therapies such as steroids, immunomodulators or biologicals.
2. Monotherapy immunosuppression (excluding biologicals): patient only receives a steroid or other immunomodulator, but not a biological. For example: patient receives azathioprine or prednisone single therapy.
3a. Monotherapy biological: patient only receives a biological such as adalimumab, infliximab, ustekinumab, vedolizumab et cetera.
3b. Monotherapy TNF-α inhibitor.
4. Combination immunosuppression (excluding biologicals): patient receives two or more immunosuppressives, but not a biological. For example: patient receives azathioprine and prednisone.
5a. Combination biological + other immunosuppression: patient receives a biological and either an immunomodulator or steroid. For example: patient receives adalimumab and azathioprine.
5b. Combination TNF-α inhibitor + other immunosuppression.

Systemic medication at the day of first vaccination: any of the above categories at the time of first vaccination.

Systemic medication during the vaccination period: the highest number category after the first vaccination until the final dose was given.

2.4. Statistical analyses

A Chi-squared test was used to compare seroprotection rates. Univariate binary logistic regression was used to identify factors that could predict early response. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) was used for the analyses and GraphPad Prism 9 for graphs. *P*-values of $\leq$ 0.05 were considered statistically significant. Missing data were not imputed.

3. Results

30 patients with IBD were included for analyses in both the modified and the standard schedule groups. Patient characteristics are shown in Table 1. Half of all patients, 17 (57 %) and 13 (43 %) in the modified and standard schedule groups respectively, had no systemic immunosuppressive therapy at the day of first vaccination.

In the modified schedule group, seroprotection rates were 28.6 %, 70.0 %, 82.8 % and 86.2 % after the first (double dose), second, third and additional vaccinations. Seroprotection rates were 58.6 %, 82.1 % and 88.9 % after the second, third and additional vaccinations in the standard schedule group; no titers were measured after the first dose in the standard schedule. There were no statistically significant differences in seroprotection rates between both groups (Fig. 1). Anti-HBs GMTs were 84.8 (95 %CI: 38.7–185.8) IU/L and 120.5 (95 %CI: 56.0–259.1) IU/L at the last titer check in patients who completed the vaccination schedule with the modified and the standard schedule respectively (see Fig. 2). Note however that titers were not checked in the majority of patients (n = 16) from the standard schedule group after their final vaccination as the schedule did not include a titer check after the final vaccination if the initial titer showed seroprotection. Titers were missing from 2 patients in the modified schedule group after the first vaccination and 1 patient did not complete the schedule. In the standard schedule group, there were no titers measured in 1 patient, 1 patient had no titers measured after the third vaccine despite being seronegative and 1 patient did not complete the schedule after the first two vaccine doses and a seronegative status.

Table 1
patient characteristics.

	Modified schedule	Standard schedule
Total number of subjects	30	30
Mean age (SD)	47 (17,1)	39 (13,1)
Male sex	33 %	50 %
Inflammatory bowel disease type		
Crohn's disease, n (%)	16 (53)	19 (63)
Colitis Ulcerosa, n (%)	13 (43)	11 (37)
Microscopic colitis, n (%)	1 (3)	0 (0)
Systemic immunosuppressive medication at the day of first vaccination		
No medication, n (%)	17 (57)	13 (43)
Monotherapy immunosuppression (excl. biological), n (%)	12 (40)	10 (33)
Monotherapy biological, n (%)	0 (0)	2 (7)
Monotherapy TNF-α inhibitor, n (%)	0 (0)	2 (7)
Combination immunosuppression (excl. biological), n (%)	1 (3)	2 (7)
Combination biological + other immunosuppression, n (%)	0 (0)	3 (10)
Combination TNF-α inhibitor + other immunosuppresion, n (%)	0 (0)	2 (7)
Systemic immunosuppressive medication during the vaccination period		
No medication, n (%)	2 (7)	0 (0)
Monotherapy immunosuppression (excl. biological), n (%)	6 (20)	10 (33)
Monotherapy biological, n (%)	13 (43)	12 (40)
Monotherapy TNF-α inhibitor, n (%)	5 (17)	7 (23)
Combination immunosuppression (excl. biological), n (%)	1 (3)	1 (3)
Combination biological + other immunosuppression, n (%)	8 (27)	7 (23)
Combination TNF-α inhibitor + other immunosuppresion, n (%)	5 (17)	6 (20)

To identify factors that could predict early response (i.e. seroprotection after a single vaccination with a double dose of Fendrix) we performed univariate binary logistic regression (Table 2) and found that lower age was significantly associated with an early response (P = 0.046). 62.5 % of patients (5 out of 8) below age 35 years had early response. Patient sex, type of IBD (Crohn's, ulcerative colitis or microscopic colitis) or type of immunosuppression at the first day of vaccination was not associated with early seroprotection.

4. Discussion

In this retrospective cohort study we show that both the modified and standard Fendrix HBV vaccination schedules resulted in high seroprotection rates against hepatitis B infection. One-third of patients with IBD achieved seroprotection after one double dose Fendrix and young age was associated with obtaining a successful early response in this group. There was no difference in final seroprotection rates after completion of the vaccination schedule between the modified and standard schedule groups.

We confirm the findings from a recent randomized clinical trial that showed high rates of seroprotection with anti-HBs $\geq$ 10 IU/L in 67 % and 88 % of patients receiving three and four doses of Fendrix respectively [7]. Seroprotection rates in our study are considerably higher than the pooled rate of 61 % that was identified in a previous meta-analysis of HBV vaccination in patients with IBD [5]. Fendrix may cause high seroprotection rates in immunocompromised patients due to the addition of the AS04C adjuvant, a Toll-like receptor 4 agonists, thought to increase immunogenicity of the HBsAg, however we have not performed a direct comparison of antibody responses between Fendrix and other HBV vaccines in patients with IBD. Nevertheless, a previously published clinical trial showed that single doses of Fendrix were as efficacious (regarding antibody responses) as double doses of the widely used Engerix-B vaccine [7]. Larger prospective studies are needed to establish whether Fendrix is superior to other HBV vaccines in immunocompromised patients, however initial data seems to support it.

The 28.6 % seroprotection rate after only one double dose Fendrix in the modified schedule group is interesting, as it suggests

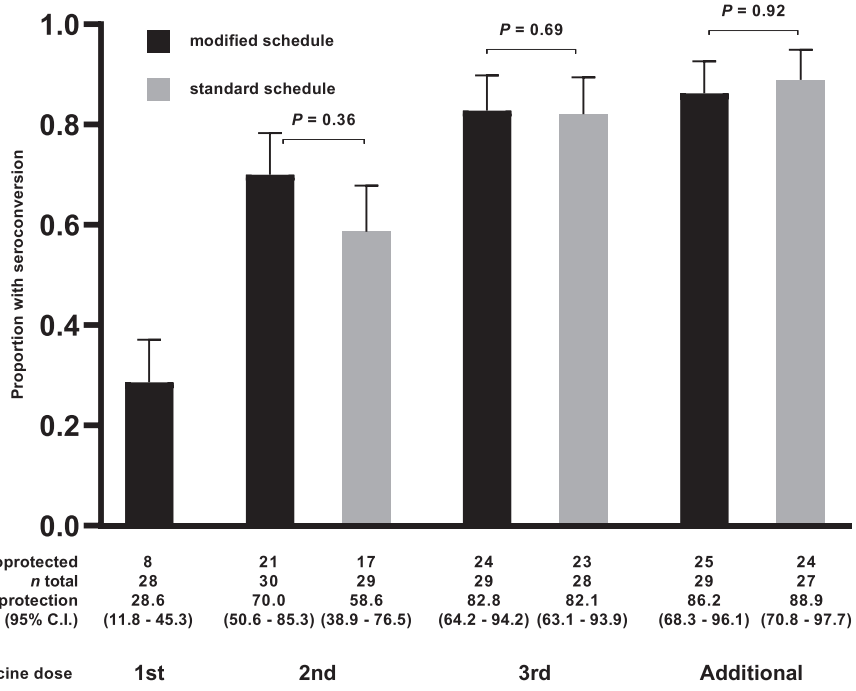

Fig. 1. Seroprotection rates. Average seroprotection rates for patients vaccinated with the modified (black) and standard schedule (grey) with standard error of the mean. Numbers of patients included for analyses are shown in the table below the graph.

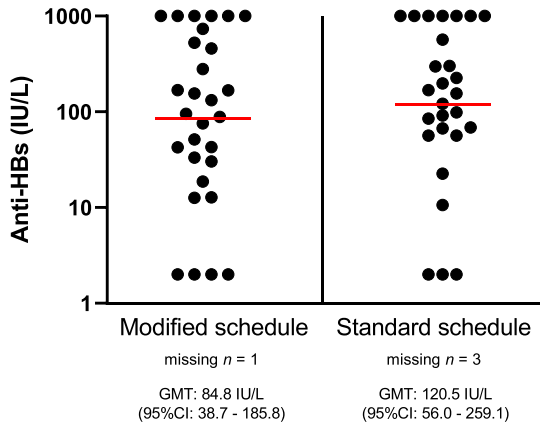

Fig. 2. Anti-HBs titers at final measurements Titers of patients after completion of the vaccination schedule. Geometric mean titers (GMT) are shown with 95 % confidence intervals (95 %CI).

that a substantial proportion of patients with IBD could benefit from only a single vaccination, reducing the time and dose needed to achieve seroprotection, which is relevant in this patient group as often there is little time between first vaccination and the start of immunosuppressive therapy. This early response rate may even be higher when selecting only younger patients for the modified schedule as 62.5 % of patients below age 35 years obtained early seroprotection in our study. In addition, rapid achievement of seroprotection against HBV is especially important in patients with IBD when bowel surgery, blood transfusions and repeated endoscopy are anticipated (factors that may increase HBV infection risk) because of ongoing severe IBD [10,11] or when protection against reactivation of chronic or occult HBV infection is warranted before initiation of systemic immunosuppression [12].

The study has several limitations. We did not obtain data on the duration of protective antibody titers. Previously, a loss of protective antibodies was observed in 20 % of patients with IBD that received four single doses of Fendrix at timepoints 0, 1, 2 and 6 months [7]. However, waning of antibody titers may not necessarily reflect loss of immune memory. Another limitation is the absence of a titer check after the first vaccination in the standard schedule group, which complicates comparison of early seroprotection with the modified schedule. Furthermore, we did not formally assess potential adverse events of an initial double dose of Fendrix, although we did not have patients reporting severe adverse events. Moreover, apparent absence of association of clinical factors with early response (Table 2), such as systemic immunosuppression at first vaccination, should be interpreted with caution due to small sample sizes. Lastly, our study showed high rates of anti-HBs conversion, however protection against actual HBV infection was not assessed. None of the included patients were reported to have an active hepatitis B infection at the time of our analyses.

In conclusion, high seroprotection rates for HBV can be achieved by vaccinating immunocompromised patients with Fendrix. An initial double dose of Fendrix does not result in higher seroprotection rates as compared to a normal schedule, however an initial double dose of Fendrix may be considered when quick seroprotection is warranted in patients with an increased risk of HBV infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Chen D, Luo S, Ben Q, Lu L, Wan X, Wu J. Prevalence of hepatitis B and C and factors for infection and nonimmune in inflammatory bowel disease patients in China. Eur J Gastroenterol Hepatol 2017;29(5):509–15. https://doi.org/10.1097/MEG.0000000000000838.

[2] Huang ML, Xu XT, Shen J, Qiao YQ, Dai ZH, Ran ZH. Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: A retrospective study. J Crohn's Colitis 2014;8(4):282–7. https://doi.org/10.1016/j.crohns.2013.08.017.

[3] Belle A, Bronowicki J-P, Peyrin-Biroulet L. Reactivation of Viral Hepatitis in Immunosuppressed Patients: An Ounce of Prevention Is Worth a Pound of Cure. Gastroenterology 2011;140(1):360–2.

[4] Rahier JF, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis, Jun. 2014;8(6):443–68. 10.1016/j.crohns.2013.12.013.

[5] Jiang H-Y, Wang S-Y, Deng M, Li Y-C, Ling Z-X, Shao Li, et al. Immune response to hepatitis B vaccination among people with inflammatory bowel diseases: A systematic review and meta-analysis. Vaccine 2017;35(20):2633–41.

[6] Gisbert JP, Menchén L, García-Sánchez V, Marín I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2012;35(12):1379–85. https://doi.org/10.1111/j.1365-2036.2012.05110.x.

[7] Chaparro M, Gordillo J, Domènech E, Esteve M, Barreiro-de Acosta M, Villoria A, et al. Fendrix vs Engerix-B for Primo-Vaccination Against Hepatitis B Infection in Patients With Inflammatory Bowel Disease: A Randomized Clinical Trial. Am J Gastroenterol 2020;115(11):1802–11.

[8] de Silva TI, Green ST, Cole J, Stone BJ, Dockrell DH, Vedio AB. Successful use of Fendrix in HIV-infected non-responders to standard hepatitis B vaccines. J Infect 2014;68(4):397–9.

Table 2
Association of clinical variables with early response.

	Response after initial double dose Fendrix N = 8	No response after initial double dose Fendrix N = 20	Univariate analysis, P value
Mean age (SD)	35 (10,1)	50 (17,5)	0.046
Male sex	3 (37.5 %)	6 (30 %)	0.702
Inflammatory bowel disease type			
Crohn's disease, n (%)	4 (50 %)	11 (55 %)	0.932
Colitis Ulcerosa, n (%)	4 (50 %)	8 (40 %)	0.707
Microscopic colitis, n (%)	0 (0 %)	1 (5 %)	1.000
Systemic medication at the day of first vaccination			
No medication, n (%)	5 (62.5 %)	11 (55 %)	0.976
Monotherapy immunosuppression (excl. biological), n (%)	3 (30 %)	8 (40 %)	0.824
Monotherapy biological, n (%)	0 (0 %)	0 (0 %)	–
Monotherapy TNF-α inhibitor, n (%)	0 (0 %)	0 (0 %)	–
Combination immunosuppression (excl. biological), n (%)	0 (0 %)	1 (4,5 %)	1.000
Combination biological + other immunosuppression, n (%)	0 (0 %)	0 (0 %)	–
Combination TNF-α inhibitor + other immunosuppresion, n (%)	0 (0 %)	0 (0 %)	–

[9] Machiels JD, Braam EE, van Bentum P, van Vugt M, de Vries-Sluijs TEMS, Schouten IWEM, et al. Vaccination with Fendrix of prior nonresponding patients with HIV has a high success rate. AIDS 2019;33(3):503–7. https://doi.org/10.1097/QAD.0000000000002085.

[10] Tolentino YFM, Fogaça HS, Zaltman C, Ximenes LLL, Coelho HSM. Hepatitis B virus prevalence and transmission risk factors in inflammatory bowel disease patients at Clementino Fraga Filho university hospital. World J Gastroenterol May 2008;14(20):3201–6. https://doi.org/10.3748/wjg.14.3201.

[11] van Remoortel H, Borra V, de Buck E, Compernolle V, Vandekerckhove P. Is an endoscopic examination associated with transfusion-transmissible infections? A systematic review and meta-analysis. Transfusion Feb. 2018;58(2):507–19. https://doi.org/10.1111/trf.14416.

[12] Hou JK, Velayos F, Terrault N, Mahadevan U. Viral hepatitis and inflammatory bowel disease. Inflamm Bowel Dis Jun. 2010;16(6):925–32. https://doi.org/10.1002/ibd.21284.