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BRIEF REPORT

Evaluation of the immune response to hepatitis B vaccine in patients on biological therapy: results of the RIER cohort study

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Abstract

To evaluate the response to hepatitis B virus (HBV) vaccine in patients on biological therapy. Adults with autoimmune inflammatory diseases on biological therapy such as anti-TNFα, rituximab, tocilizumab, abatacept, or anakinra were included. Hepatitis B surface antibody (anti-HBs) was measured by ELISA before and after vaccination. Seroconversion was considered when an anti-HBs titer > 10 mIU/mL was achieved. The effect of treatment on the immunoprotective state was studied. The response was compared with that obtained in patients on synthetic disease modifying anti-rheumatic drugs (DMARDs) and healthy controls. A total of 187 patients on biologicals, 48 on synthetic DMARDs, and 49 on healthy controls were analyzed. More than 80% of patients on biologics responded to the vaccine but required more boosters and second vaccine series. Patients who achieved seroconversion were younger than those who did not (47.10 ± 12.99 vs. 53.18 ± 10.54 years, $p = 0.012$). Being on etanercept or golimumab was associated with seroconversion, while being on rituximab was not. Seroconversion was achieved in 93.75% of patients on synthetic DMARDs and 97.96% of healthy controls. The seroconversion rate in the biologics group was lower than in the synthetic DMARD group ($p = 0.043$) and tended to be lower than in the healthy group ($p = 0.056$). In patients on biological therapy, a high rate of HBV vaccine response can be achieved when a complete vaccination schedule is administered. Vaccination while not on biological agents reduces the requirement for boosters and revaccination.

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Key points:
- *Patients on biological therapy can achieve high rates of immune response to HBV vaccine when complete vaccination schedules are administered.*
- *However, to achieve such a high seroconversion rate, more boosters and second vaccination series are required.*
- *This supports the proposal already made to provide HBV vaccination to all patients with an autoimmune inflammatory disease after the diagnosis is made and not when the use of a biological treatment is under consideration.*

Keywords Anti-TNF · Biological therapy · Hepatitis B virus · Rituximab · Vaccination

Introduction

Hepatitis B virus (HBV) infection is a preventable disease that can increase morbidity in patients with autoimmune inflammatory rheumatic diseases (AIRDs) by causing hepatic injury [1]. Vaccination against HBV in these patients is recommended when the risk of contracting the infection is high, such as travel/residence in HBV-endemic countries and risk of exposure [2, 3]. Other immunosuppressed patients, such as those with inflammatory bowel disease (IBD), are encouraged to be vaccinated against HBV, even they do not present other risk factors [4, 5]. Furthermore, vaccination against HBV is included in the childhood immunization schedule of many countries since more than 20 years.

However, in patients with autoimmune diseases, vaccine effectiveness (VE) is not clear, as it could be modified due to the disease per se and/or immunosuppressive drugs.

The aim of our study was to determine whether the HBV vaccination effectiveness in patients with AIRDs is affected by the biological therapy, and if it depends on the type of biological disease modifying anti-rheumatic drug (DMARD) used in routine clinical practice. We also wanted to know whether demographic characteristics and concomitant treatment with corticosteroids and/or synthetic DMARDs would impact the VE.

Materials and methods

Subjects older than 18 with AIRDs, psoriasis (PsO), or inflammatory bowel disease (IBD) were included. Patients had to be on biological DMARD therapy, with the choice of biological agent depended on the patient's characteristics and clinical parameters. Patients who changed their biological DMARD between baseline and the final serological tests were excluded from the analysis. Data on concomitant treatments with synthetic DMARDs and corticosteroids were recorded. Patients with serological data of chronic HBV or active HBV markers were excluded.

A control group including patients with similar diagnoses, who were on synthetic but not biological DMARDs, was also recruited.

Vaccination status was recorded from primary care databases. Patients received a first vaccination course, booster, or second course depending on the vaccination status before entering the study and the vaccine response (Fig. 1). In accordance with the recommendations, whenever a second vaccination series was needed, the booster was considered the first dose of the revaccination series.

Hepatitis B surface antibody (anti-HBs) was measured by a commercial ELISA routine test kit. The patient was considered responder when anti-HBs titer after vaccination was > 10 mIU/mL. A subject was considered a nonresponder when, despite two correctly administered full courses of HBV vaccine, they failed to cross an anti-HBs threshold of 10 mIU/mL, determined at least 4 weeks after the last vaccine dose.

In order to compare the immune responses obtained in patients with those achieved in healthy people, we also retrospectively recorded data from Infanta Sofía University Hospital healthy staff who had already been vaccinated.

Details about methods and statistics are available as electronic supplementary material.

Results

Two hundred and nineteen patients on biological therapy were included. Twenty-three were anti-HBc-positive and so were excluded; a further seven did not complete the first vaccination series and two others stopped the biological DMARD just before being vaccinated, so all were also rejected. The remaining 187 were then analyzed.

Figure 2 shows the number of patients vaccinated before entering the study, upon entering the study, patients who needed a booster and second cycle, as well as the number of responders in each category. Twenty patients did not complete the vaccination schedule, all of them needing revaccination.

Forty-eight patients on synthetic but not biological DMARDs and 49 healthy controls were recruited. Demographic data, diagnosis, and treatments are shown in Table 1. Thirty-three patients (17.65%) on biologics were on corticosteroids and 91 (48.66%) were on synthetic DMARDs.

One hundred and fifty-three (81.82%) of the 187 patients on biological therapy achieved seropositivity. When we

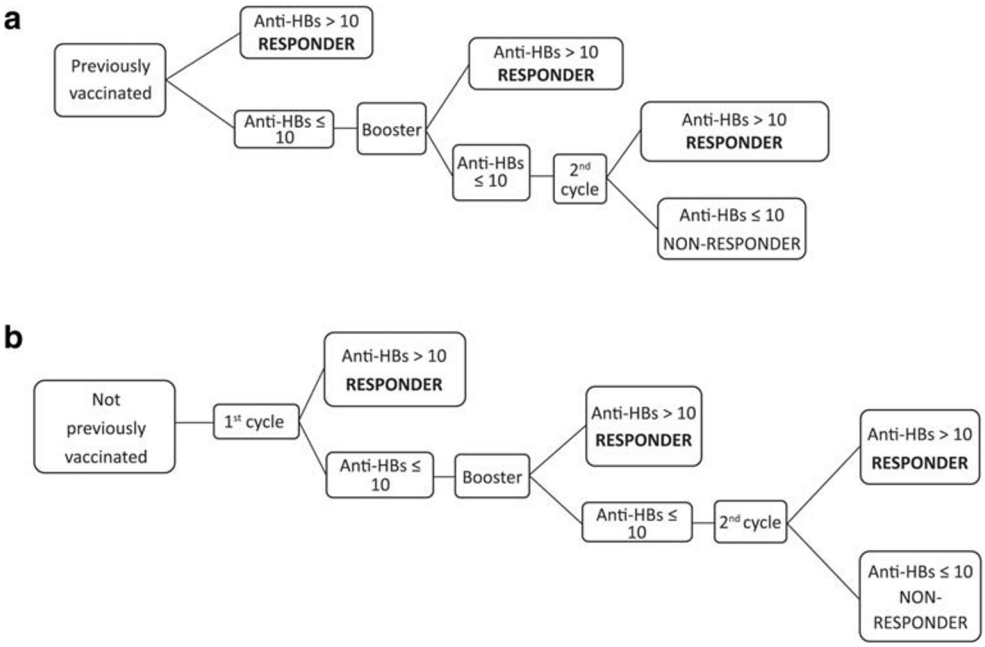

Fig. 1 Vaccination schedule depending on the vaccination status before entering the study. **1a** Patients already vaccinated before entering the study. **1b** Patients who received a primary vaccination course upon entering the study

analyzed the percentage of responders in the group who completed the full course ($n = 167$), this increased to 89.30%.

Responders were younger than nonresponders (47.10 ± 12.99 vs. 53.18 ± 10.54 years, $p = 0.012$).

Neither concomitant treatment with synthetic DMARDs nor corticosteroids impaired the response: 81.69% of patients on DMARDs and 88.00% of those not on DMARDs were responders ($p = 0.222$), while 86.36% of subjects on corticosteroids vs. 78.79% of those not on steroid treatment became seropositive ($p = 0.285$).

When we studied the response in Pso and IBD, we found that all Pso patients respond to the first vaccine series while 2 IBD patients responded to the first cycle, one to the booster and the reaming three patients stayed seronegative, without receiving revaccination.

Table 2 shows the proportion of responders according to each biological agent. Patients on etanercept were more likely to respond to the vaccine than those subjects on the other biologics (OR, 3.074, 95% CI, 1.124–8.405, $p = 0.023$), while most patients on rituximab were nonresponders (OR, 0.064,

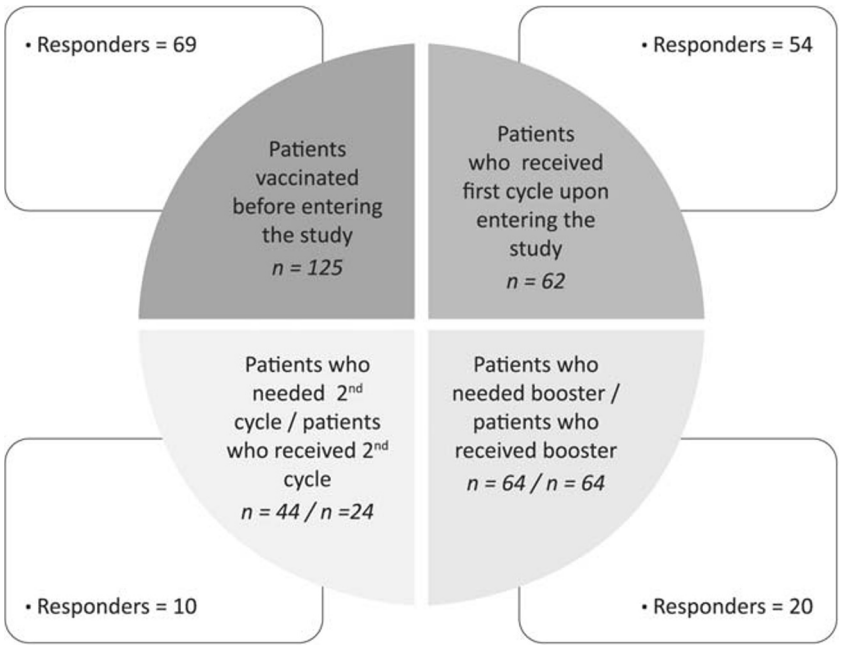

Fig. 2 Data showing response in patients on biological therapy. Patients were categorized depending on the vaccination status (previously vaccinated, first vaccinated when entering the study, booster required, revaccination required)

Table 1 Demographic data, diagnosis, and biological treatment of participants

	Patients on biological DMARDs $n = 187$ (%)	Patients on synthetic DMARDs $n = 48$ (%)	Controls $n = 49$ (%)
Sex			
Male	73 (39.04)	16 (33.33)	9 (18.37)
Female	114 (60.96)	32 (66.67)	40 (81.63)
Age (years)	48 ± 13*	54 ± 12*§	39 ± 9
Diagnosis			
RA	57 (30.48)	25 (52.08)	–
SpA	73 (39.04)	6 (12.50)	–
PsA	30 (16.04)	13 (27.08)	–
PsO	9 (4.81)	1 (2.08)	–
IBD	6 (3.21)	–	–
Others[a]	12 (6.42)	3 (6.25)	–
Biological DMARD			
Etanercept	58 (31.02)	–	–
Adalimumab	55 (29.41)	–	–
Infliximab	22 (11.76)	–	–
Golimumab	17 (9.09)	–	–
Rituximab	14 (7.49)	–	–
Tocilizumab	9 (4.81)	–	–
Certolizumab	8 (4.28)	–	–
Abatacept	3 (1.60)	–	–
Anakinra	1 (0.53)	–	–

RA rheumatoid arthritis; *SpA* spondyloarthritis; *PsA* psoriatic arthritis; *PsO* psoriasis; *IBD* inflammatory bowel disease; *DMARD* disease modifying anti-rheumatic drug

* Older than healthy controls, $p < 0.001$

§ Older than patients on biological DMARDs, $p = 0.015$

a Others include five patients with undifferentiated arthritis, two with juvenile idiopathic arthritis, one with Still's disease, one with amyloidosis, one with polymyalgia rheumatic, one with systemic lupus erythematosus, and one with Sjogren's syndrome

95% CI, 0.019–0.222, $p < 0.001$). Patients on rituximab were older than those not receiving this drug (56.0 ± 9.6 vs. 47.6 ± 12.8, $p = 0.017$), but the association between rituximab and worse response remained after adjusting for age (OR, 0.077, 95% CI, 0.019–0.222, $p < 0.001$).

Sixteen of the 48 patients (33.33%) on synthetic DMARDs group had been vaccinated before entering the study. Six patients needed a booster and four a second vaccination series. At the end of the study, 45 patients (93.75%) became responders.

In the healthy control group, 48 of the 49 subjects (97.96%) responded after one vaccine cycle. The remaining subject did not receive any other dose.

The response rate in patients on biological therapy was lower than in patients on synthetic DMARDs ($p = 0.043$) and also lower than in healthy participants ($p = 0.005$), while responses did not differ between healthy participants and patients on synthetic DMARDs. When we adjusted the analysis for age, we found a high tendency, but not statistically significant difference, between the immune response in healthy controls and patients on biologics ($p = 0.056$). Differences between subjects on biologics and those on synthetic DMARDs remained significant.

Table 2 Number of responders depending on the biological agent

Biological agent	Responders, *n* (%)	*p*
Etanercept, $n = 58$	53 (91.38)	***0.023***
Adalimumab, $n = 55$	47 (85.45)	0.405
Infliximab, $n = 22$	15 (68.18)	0.085
Golimumab, $n = 17$	17 (100.00)	***0.046***
Rituximab, $n = 14$	4 (28.57)	***< 0.001***
Tocilizumab, $n = 9$	7 (77.78)	0.668
Certolizumab, $n = 8$	8 (100.00)	0.354
Abatacept, $n = 3$	2 (66.67)	0.454
Anakinra, $n = 1$	0 (0.00)	0.182

Significant *p* values are highlighted in bold italics

Sixty-four patients on biologics and six on synthetic DMARDs needed a booster (34.22% vs. 12.50%, $p = 0.003$), while 44 subjects in the former group and four in the latter required a second vaccination series (23.53% vs. 8.33%, $p = 0.023$).

Discussion

To the best of our knowledge, this is one of the largest cohort studies of patients with autoimmune inflammatory diseases to investigate the immune response to HBV vaccination in patients on biological therapy. We found that, even while on biologics, a high seroconversion rate could be achieved with a correct and complete vaccination schedule.

The response to the HBV vaccine has long been studied, finding response rates around 60%, with older age and immunosuppressive therapy associated with lower seroconversion rates.

In a small cohort of 22 patients with RA, not on biologics, Elkayam et al. found that HBV vaccination produced antibodies in 68% of patients [1]. Intongkam et al. vaccinated 46 RA patients and achieved a 64% seroconversion rate [6]. In both studies, the authors administrated just one vaccination cycle and obtained results that are quite similar to ours when we consider only those who responded to a first cycle ($n = 123$ patients, 65.78%).

As we observed, seroconversion rates increase in patients on DMARDs when booster and second series are administered. These findings are supported by a study by Gisbert et al. in a cohort of 241 patients with IBD, where they found

seroconversion in 59% of patients after the first vaccination cycle, increasing to 79% after administering the second series when needed [7].

In our study, we found that among patients on biological therapy, older age was associated with a worse immune response. These results are consistent with others previously described [6, 7].

With respect to the effect on the immune response of each of the biological agents, we found that patients on etanercept or golimumab obtained better responses, while infliximab did not impair the immune response, as reported by Pratt et al. who, in a recent study performed in IBD patients, found that patients on infliximab were significantly less likely to achieve seroconversion [4].

It is important to highlight the poor results obtained in patients on rituximab. In our series, only 4 of the 14 patients on rituximab achieved seroconversion, and just 2.61% of responders were on rituximab. Intongkam et al. found comparable results. In their study, responders to the HBV vaccine were less likely to be on rituximab (only 2 of the 8 patients receiving rituximab responded and only 2 of the 29 responders were on this drug) [6]. Nevertheless, these results must be interpreted with caution due to the small sample size when we studied the biological agents individually (22 patients on infliximab, 17 on golimumab, and 14 on rituximab).

Impairment of the vaccine response due to biologic therapy has been previously described. In patients with IBD on anti-TNF, treatment with anti-TNF was associated with worse results (46% of those on anti-TNF vs. 62% of those who were receiving azathioprine, mercaptopurine, or methotrexate, but not an anti-TNF, $p < 0.050$) [7].

Moreover, in a meta-analysis performed to investigate the rate of seroconversion after HBV vaccination and its predictive factors in patients with IBD, the authors found 13 studies with seroconversion rates of between 34% and 78%. Patients who did not receive corticosteroids or synthetic DMARDs were more likely to show a good immune response than those who did (relative risk (RR), 1.33; 95% CI, 1.08–1.63), and even better than in subjects on anti-TNF (RR, 1.57; 95% CI, 1.19–2.08) [8].

Our results agree with those previously published, although we only found a tendency towards a better response in the healthy controls when this was analyzed after adjusting for age.

There was a significantly higher requirement for boosters and revaccination in the biologics group than in the synthetic DMARD group. We found that 19 patients on biological therapy did not receive revaccination, remaining unprotected against HBV. This lack of compliance is due, in part, to the prolonged duration of the vaccination process. Thus, vaccination at disease onset, when the patients are younger and probably still only on synthetic DMARDs and when a faster response will likely be achieved, would avoid the need for boosters and revaccinations that increase costs and lead to vaccination schedules that are longer and difficult to adhere to.

Nevertheless, like other authors [9], we believe in the advantages of offering HBV vaccine to patients after an AIRD has been diagnosed, as more than 60% of our patients were not vaccinated before entering the study. Efforts must be made to implement immunization against HBV in these patients.

The question of when to check the seroprotection status of patients on immunosuppressive treatment who have been already vaccinated has not yet been resolved, although measurement of antibody titers every 2–3 years, followed by a booster if anti-HBs is < 10 mIU/mL, has been proposed [5, 10].

It is also important to stress that nonresponder status should be formally recorded, due to the possibility of using post-HBV exposure measures in case of exposure to HBV [11].

One limitation of our study was that groups were not homogenous in terms of age. Patients were recruited from outpatients, so they reflected the reality of daily clinical practice in our area. Data from healthy controls were retrospectively collected from Infanta Sofía University Hospital, which was opened in 2008, with a considerable number of staff being younger than 40. For this reason, the median age of the control group was not surprising. Thus, a comparison between more homogenous populations might improve the accuracy of our findings.

Unless the sample size is large enough to evaluate the vaccination response in the whole group, a larger study may lead to a more accurate comparison between responses to the vaccine depending on the type of biological agent.

In summary, patients with AIRDs on biological therapy will show a poorer immune response as they get older and will need booster and a second vaccination series more frequently than when they are on synthetic DMARDs only. Nevertheless, complete vaccination schemes will provide high seroconversion rates in these patients.

We consider that early HBV vaccine administration will benefit patients with AIRDs.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Patricia Richi, Oriol Alonso, María Dolores Martín, Laura González-Hombrado, Teresa Navío, Marina Salido, Jesús Llorente, Cristina Andreu-Vázquez, Cristina García-Fernández, Ana Jiménez-Diaz, Leticia Lojo, Laura Cebrián, IsraelThuissard-Vasallo, María José Martínez de Aramayona, Tatiana Cobo, Marta García-Castro, Patricia Castro, Mónica Fernández-Castro, Óscar Illera, Martina Steiner, and Santiago Muñoz-Fernández. Patricia Richi wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Patricia Richi declares she has received research grants from Sociedad de Reumatología Comunidad de Madrid (SORCOM)/MSD and Pfizer. Santiago Muñoz-Fernández declares he has received research grants from Sociedad de Reumatología Comunidad de Madrid (SORCOM)/MSD and Pfizer. The rest of authors declare that they have no conflict of interest.

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