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SHORT REPORT

Hepatitis B vaccination associated with low response in patients with rheumatic diseases treated with biologics

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ABSTRACT

Background Hepatitis B virus (HBV) vaccination is recommended for non-immunised patients with rheumatic diseases starting biological disease-modifying antirheumatic drugs (bDMARDs). There is some evidence that HBV vaccination is effective in patients under conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), but it is currently unclear whether this also applies to bDMARDs.

Objectives To assess the efficacy and safety of HBV vaccination in patients with inflammatory arthritides treated with bDMARDs.

Methods A prospective cohort with inflammatory arthritides treated with bDMARDs, negative for anti-HBs and anti-HBc and never vaccinated for HBV was recruited. Engerix B was administered at 0, 1 and 6 months and anti-HBs was reassessed ≥1 month after last dose. Response was defined as anti-HBs≥10 IU/L and compared against vaccinated healthy controls. Disease flare, serious adverse events and immune-related disorders not previously present were recorded.

Results 62 patients, most treated with TNF inhibitors (TNFi), and 38 controls were recruited. Most patients were taking csDMARDs (67.7%) and were in remission/low disease activity (59.4%). Only 20/62 patients (32.3%) had a positive response to vaccination, in comparison to 36/38 age-matched controls (94.7%, p<0.001). Response was seen in 19/51 patients treated with TNFi (37.3%) and in 1/11 (9.1%) patients treated with non-TNFi (p=0.07), including 1/6 treated with tocilizumab (16.7%). Among TNFi, response rates ranged from 4/22 (18.2%) for infliximab to 8/14 (57.1%) for etanercept. No relevant safety issues were identified.

Conclusions HBV vaccination response in patients with rheumatic diseases treated with bDMARDs was poorer than expected. Our data reinforce the recommendation for vaccination prior to starting bDMARDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are little and conflicting data on the safety and effectiveness of hepatitis B vaccination in patients with rheumatic diseases under biological treatment.

WHAT THIS STUDY ADDS

⇒ Hepatitis B vaccine is safe, but its effectiveness may be lower than expected for patients treated with tocilizumab and TNF inhibitors, with important differences among TNF inhibitors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underline the importance to screen at-risk patients and vaccinate them before biological treatment is started.

⇒ For patients on biological treatment, alternative vaccination strategies such as double dosage (indicated for dialysis patients) might be preferable.

INTRODUCTION

Hepatitis B virus (HBV) infection is common worldwide, with an estimated prevalence of 1% in Western Europe,[1] and a recent rise in hospital admissions has been reported due to migration from Eastern Europe, where endemicity is higher.[2] Treatment with biological disease-modifying antirheumatic drugs (bDMARDs) has been associated with HBV reactivation, especially rituximab (RTX).[3] HBV vaccination is thus recommended for non-immunised patients with inflammatory arthritides (IA), in particular those at risk, starting bDMARDs.[4–6] There is some evidence that HBV vaccination is effective in patients under conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (68%–95% seroprotection[7 8] vs >85% in healthy adults[9]), but it is currently unclear whether this also applies to bDMARDs, with little and conflicting evidence available.[10–13]

We therefore aimed to assess the efficacy and safety of HBV vaccination in patients with IA treated with bDMARDs.

Table 1 Baseline characteristics of study participants

	All patients (n=62)	RA (n=31)	SpA (n=31)
Age, years (mean±SD)	56.0±9.0	56.7±9.2	55.2±8.9
Female, n (%)	37 (59.7)	28 (90.3)	9 (29.0)
Disease duration, years (mean±SD)	18.0±9.7	17.4±8.8	18.6±10.7
bDMARDs, n (%)			
TNF-inhibitor	51 (82.3)	20 (64.5)	31 (100.0)
Infliximab	22 (35.5)	10 (32.3)	12 (38.7)
Etanercept	14 (22.6)	6 (19.4)	8 (25.8)
Adalimumab	10 (16.1)	2 (6.5)	8 (25.8)
Golimumab	5 (8.1)	2 (6.5)	3 (9.7)
Tocilizumab	6 (9.7)	6 (19.4)	–
Rituximab	4 (6.5)	4 (12.9)	–
Abatacept	1 (1.6)	1 (3.2)	–
Time on current bDMARD before first HBV vaccine dose, months (mean; minimum–maximum)	75.7; 5.0–198.8	76.4; 6.5–199.8	74.9; 5–191.2
Combination with csDMARDs, n (%)	42 (67.7)	51 (82.3)	14 (45.2)
TNF-inhibitors	31 (60.8)	22 (35.5)	14 (45.2)
Tocilizumab	6 (100.0)	14 (22.6)	–
Rituximab	4 (100.0)	10 (16.1)	–
Abatacept	1 (100.0)	5 (8.1)	–
Glucocorticoids, n (%)	25 (40.3)	21 (67.7)	4 (12.9)
Prednisolone dose, mg (mean±SD if prednisolone was prescribed)	5.6±2.1	5.1±1.7	8.1±2.4
Disease activity class, n (%)			
Remission	25 (41.0)	15 (50.0)	10 (32.3)
Low	12 (19.7)	4 (13.3)	8 (25.8)
Moderate	15 (24.6)	8 (26.7)	7 (22.6)
High	4 (6.6)	3 (10.0)	1 (3.2)
Very high	5 (8.2)	0 (0.0)	5 (16.1)

bDMARD, biological disease-modifying antirheumatic drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; HBV, hepatitis B virus; RA, rheumatoid arthritis; SpA, spondyloarthritis (ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease-related spondyloarthritis); TNF, tumour necrosis factor.

METHODS

This was a prospective, single-centre, observational study conducted at our rheumatology department. We included patients diagnosed with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA) or inflammatory bowel disease-related spondyloarthritis (IBD-SpA) treated with bDMARDs, with no prior HBV vaccination history and negative serology for anti-HBs and anti-HBc. Patients were advised to take the recombinant alum-adjuvanted HBV vaccine (Engerix B) 20 µg at 0, 1 and 6 months, in accordance with national guidelines.[4] Patient recruitment took place between December 2015 and November 2018, and data collection ended in January 2021. Primary outcome was vaccine response, defined as an anti-HBs titre≥10 IU/L post vaccination. Antibody titres<10 IU/L, considered negative, were recorded as 0. Anti-HBs titre was determined in blood samples collected according to routine care, using Elecsys Anti-HBs (electrochemiluminescence immunoassay), after a minimum of 1 month past the third dose. Follow-up included in-person assessment and blood analysis every 3 months, from 3 months before first HBV vaccine dose to 3 months after the third dose. Serious adverse events (SAEs), disease flares or incident immune-related disorders were recorded.

Disease Activity Score 28-joints (DAS28) was used to assess disease activity in RA and peripheral PsA; Ankylosing Spondylitis Disease Activity Score (ASDAS) was used for axSpA, axial PsA and IBD-SpA. The following cut-offs for disease activity were used: DAS28<2.6: remission, ≥2.6 and ≤3.2: low, >3.2 and ≤5.1: moderate, >5.1: high; ASDAS<1.3: remission (inactive disease), ≥1.3 and <2.1: low, ≥2.1 and ≤3.5 high, >3.5: very high.

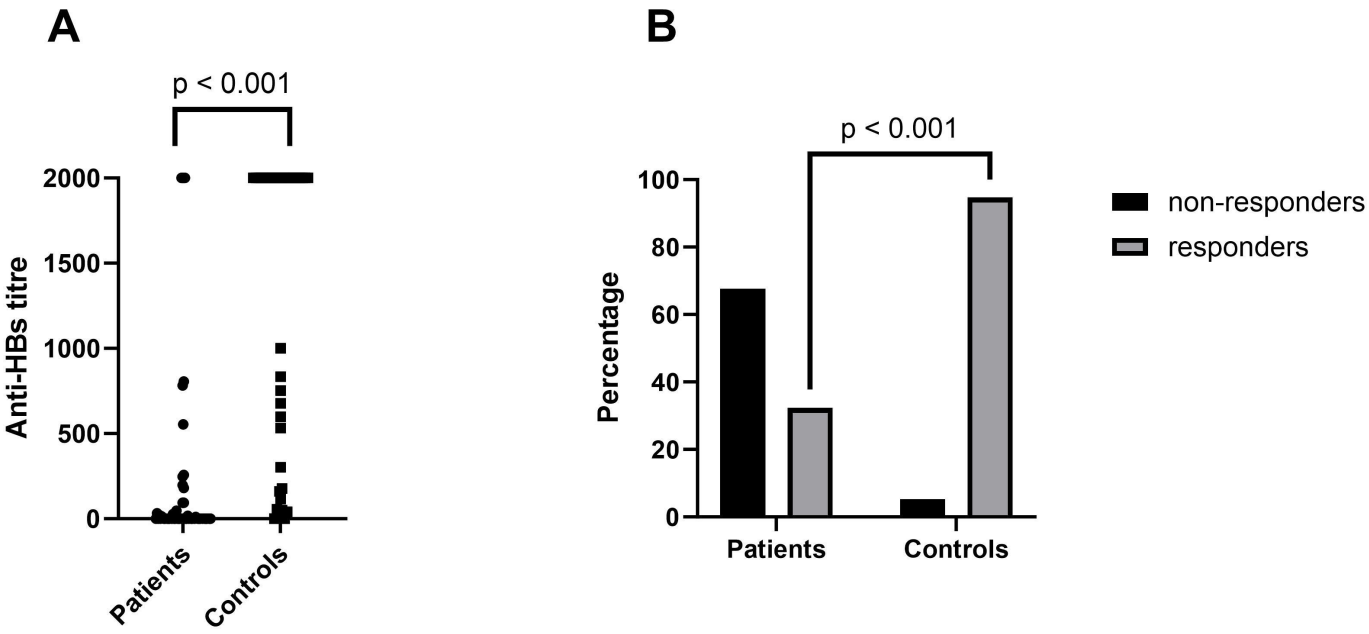

Figure 1 Anti-HBs titre (A) and percentage of response (B) after hepatitis B vaccination. Line in graph (A) represents the median of the observations.

Flare was defined as ASDAS change≥0.9, DAS28 change>1.2 or >0.6 if DAS28≥3.2, corticosteroid dose increase or non-steroidal anti-inflammatory drug prescription, occurring up to 1 month post vaccination. Clinical variables, including age, gender, diagnosis, duration of disease, duration of bDMARD treatment and comedication with csDMARDs or corticosteroids were collected.

Vaccine response was compared with that of age-matched healthy professionals undergoing Occupational Health immunization because of anti-HBs<10 IU/L. Controls received the same vaccination scheme and had anti-HBs titres determined ≥1 month after the last dose in the same laboratory.

Gender differences and proportion of responders were compared with χ^2 test. Continuous variables showing a non-gaussian distribution (such as antibody titres) were compared with the Wilcoxon rank sum test. Statistical analysis was performed using STATA V.14.2. Statistical significance was defined as α=0.05.

RESULTS

Sixty-two (31 RA; 31 SpA, consisting of 18 PsA, 12 axSpA and 1 IBD-SpA) patients and thirty-eight controls were included, matched for age (patients (mean±SD) 55.8±8.9 vs controls 52.9±5.7 years). The proportion of females in the control group (n=35, 92.1%) was significantly higher than in the patient cohort (n=37, 59.7%, p<0.001), as there were not enough male controls available to match for both age and gender. Patients' characteristics are summarised in table 1. Most patients were treated with tumour necrosis factor inhibitors (TNFi; 82.3%) and around two-thirds were taking concomitant csDMARDs (67.7%) and were in remission or low disease activity (60.7%). Only 20/62 patients (32.3%) had a positive response to vaccination, in comparison to 36/38 age-matched controls (94.7%, p<0.001, figure 1). Mean post-vaccination anti-HBs titre (± SD) was significantly lower in responding patients than responding controls (569±772 vs 1370±827 U/L, p<0.001). Response rate was 8/31 (25.8%) in RA and 12/31 (38.7%) in SpA (table 2). Response was seen in 19/51 patients treated with TNFi (37.3%), but only in 1/11 (9.1%) patients treated with non-TNFi bDMARDs (p=0.07). Within TNFi class, response rates ranged from 4/22 (18.2%) for intravenous infliximab to 8/14 (57.1%) for etanercept. Response rates for non-infliximab TNFi were 40%–57.1%. Timing of vaccination in relation to infliximab infusion was not significantly different for responders vs non-responders. However, all four infliximab-treated responders had an infusion-free period of at least 8 days before and after each vaccine (this was also the case for 7/18, 38.9% of non-responders). Twenty-five patients were concomitantly treated with prednisolone (40.3%, mean dose 5.6 mg/day) among whom there were seven responders (28.0%). Mean prednisolone dose was similar in responders (5.7±2.4 mg/day) and non-responders (5.6±2.0 mg/day). Four patients had to temporarily interrupt bDMARDs due to other intercurrences for at least one administration. Even so, all of them were non-responders.

Sixteen patients (25%) experienced disease flares: nine were mild and did not require therapy adjustment; five patients needed minor treatment/dose adjustments; and two patients had secondary failures that led to treatment switch. There were four SAEs occurring 1–4 months after the first/second dose, deemed to be unrelated to vaccination: acute diverticulitis in a patient with RA on golimumab; atrial fibrillation and urinary infection motivating

Table 2 Comparison between responding and non-responding patients

	Responders (n=20)	Non-responders (n=42)
Age, years (mean±SD)	54.0±9.1	56.9±8.9
Female, n (% in row)	13 (35.1)	24 (64.9)
Diagnosis, n (% in row)		
Rheumatoid arthritis	8 (25.8)	23 (74.2)
Spondyloarthritis	12 (38.7)	19 (61.3)
Disease duration, years (mean±SD)	15.0±8.2	19.4±10.2
bDMARDs, n (% in row)		
TNF-inhibitor	19 (37.3)	32 (62.8)
Infliximab	4 (18.2)	18 (81.8)
Etanercept	8 (57.1)	6 (42.9)
Adalimumab	5 (50.0)	5 (50.0)
Golimumab	2 (40.0)	3 (60.0)
Tocilizumab	1 (16.7)	5 (83.3)
Rituximab	0 (0.0)	4 (100.0)
Abatacept	0 (0.0)	1 (100.0)
Time on current bDMARD before first HBV vaccine dose, months (mean; minimum–maximum)	57.9; 5.0–159.9	83.5; 6.5–198.8
Combination with csDMARDs, n (%)		
TNF-inhibitors	13 (68.4)	18 (56.3)
Tocilizumab	1 (100.0)	5 (100.0)
Rituximab	–	4 (100.0)
Abatacept	–	1 (100.0)
Glucocorticoids, n (% in row)	7 (28.0)	18 (72.0)
Prednisolone dose, mg (mean±SD if prednisolone was prescribed)	5.7 (2.4)	5.6 (2.0)
Disease activity class, n (% in row)		
Remission	7 (28.0)	18 (72.0)
Low	6 (50.0)	6 (50.0)
Moderate	5 (33.3)	10 (66.7)
High	1 (25.0)	3 (75.0)
Very high	1 (20.0)	4 (80.0)

bDMARD, biological disease-modifying antirheumatic drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; HBV, hepatitis B virus.

hospitalisation, lower respiratory tract infection treated with amoxicillin-clavulanate as outpatient and one corneal ulcer, these last three in patients treated with infliximab. There were no adverse events in the control group.

DISCUSSION

Our study reports the response to a full, 3-dose vaccination schedule, in 62 previously unvaccinated patients with IA taking bDMARDs.

To our knowledge, only four published studies described the response to alum-adjuvanted HBV vaccine in adult patients with IA taking bDMARDs, with conflicting results.[10–13] Response rates ranged from 50% to 100% for TNFi versus 25% to 29% for RTX. Participants with IA were limited to 4 patients with RA in 2 studies[10 11] and 20 SpA in another.[12] The largest cohort of patients with rheumatic diseases vaccinated for HBV (n=187) was published by Richi *et al*.[13] Significantly lower responses for IFX were found by Solay *et al*[11] (17% vs 89% with etanercept) and Richi *et al*[13] (68% vs 85%–100% with other TNFi).

The results from our study show a lower response rate to the HBV vaccine than previously reported. Furthermore, these results may suggest a difference in vaccination response between patients treated with infliximab and non-infliximab TNFi, which remains to be confirmed. This might be related to the different pharmacokinetics

of these drugs and timing of vaccination in relation to infliximab infusion, which is likely to influence response, as serum drug levels decrease after infusion until they reach a trough level. RTX is known to impair the response to other vaccines[6]; consistently, none of the four patients treated with this drug responded. On the other hand, only 1/6 (16.7%) patient taking tocilizumab responded, contrasting with 78% response rate reported by Richi *et al*. Our study is the second only to report HBV-vaccine response under this IL-6 inhibitor and raises concerns that it may cause a larger impact than previously thought. Since IL-6 is critical for germinal center (GC) interactions,[14] it is conceivable that its blockade impairs response to GC-dependent vaccines such as HBV. It was not possible to adjust for potential confounders of the effect of bDMARDs on vaccine response, such as diagnosis, disease activity, csDMARDs or corticosteroid comedication, considering the limited sample size. Older age has been associated with worse HBV vaccination response[7] but the age-matched controls in our study had a significantly larger response rate and higher antibody titres than patient respondents, further supporting that bDMARDs impair HBV response. We could not match controls for gender, but unlike age this is not expected to play a significant role on vaccine response.

We present the second largest cohort of bDMARD-treated patients with IA receiving alum-adjuvanted HBV vaccine, and the first to compare vaccine response with age-matched controls. It is also the second (and largest) reporting safety assessment during the follow-up. Despite this context, sample size is still the most important limitation of our study. It did not allow for enough statistical power to perform logistic regression for vaccine response on individual variables in order to adjust for confounding. On the other hand, disease flares were rare, making it hard to establish an association with the vaccine. Another limitation was the fact that we were unable to match the patient and control groups for both age and gender. This was related to the fact that most control subjects recruited from our Occupational Health Department were middle-aged women. There were, thus, not enough male subjects to include, while maintaining adjustment for age. In addition, some subjects had previously been vaccinated and/or were immune, and thus not eligible for inclusion.

In conclusion, HBV vaccination response in patients with IA treated with bDMARD was poor and lower than in healthy age-matched controls. Vaccination was overall safe but there were two severe flares and four SAE that led to treatment switch/interruption, although causal association is unlikely. Our data reinforce the recommendation for HBV vaccination prior to starting bDMARDs, possibly even as soon as the diagnosis is established. Alternative HBV vaccination strategies should be investigated in patients already treated with bDMARDs, such as increased vaccine dosage,[15] different adjuvants[16] or temporary csDMARD/bDMARD interruption.[17]

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Correction: *Hepatitis B vaccination associated with low response in patients with rheumatic diseases treated with biologics*

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