CONCISE REPORT

Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis

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Background: Hepatitis B infection and vaccination against it have been implicated in the potential triggering or flare of some autoimmune diseases, including rheumatoid arthritis (RA). However, the safety of hepatitis B vaccination in patients with pre-existing RA is not known.
Objectives: To assess the safety and antibody response of immunisation with a recombinant DNA hepatitis B vaccine in patients with RA.
Patients and methods: The study comprised 44 patients with RA, of whom 22 received three doses (the second and third dose being given after one and six months) of a recombinant DNA hepatitis B vaccine (study group) and 22 did not receive the vaccine (control group). Both groups had comparable proportions of women and similar mean age (51 years). Clinical assessment before and two and seven months after the first immunisation included evaluation of daytime pain with a 10 cm visual analogue scale, duration of morning stiffness, and number of tender and swollen joints. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were measured at each visit. Antibodies to hepatitis B surface antigen (HBsAg) were determined by a commercial enzyme linked immunosorbent assay (ELISA) test kit.
Results: Hepatitis B vaccination was not associated with an appreciable deterioration in any clinical or laboratory measure of disease. The measures of disease activity of the patients and controls during the study period did not differ significantly: p=0.76 for daytime pain, p=0.1 for morning stiffness, p=0.24 and p=0.3 for tender and swollen joints respectively, p=0.08 for CRP, and p=0.12 for ESR. Fifteen of the 22 patients responded to vaccination, with an antibody level against HBsAg of 10 IU/l after seven months. Lack of response was associated with older age and higher scores of daytime pain.
Conclusions: Hepatitis B vaccination is safe in RA and produces antibodies in 68% of the patients.

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis of unknown cause. Various genetic and environmental factors have been associated with an increased risk for the development of disease.[1] Several reports describing the appearance of RA after vaccination with tetanus, rubella,[2] and hepatitis B[3–5] suggest a causal relationship. These reports raise the questions whether vaccines may induce RA and how safe are vaccines in people already diagnosed with the disease.

Hepatitis B vaccine was initially recommended for adults or children at high risk of hepatitis B virus infection.[6] It has also been suggested that immunosuppressed patients with RA who are treated with potentially hepatotoxic drug such as methotrexate should be vaccinated in order to neutralise another potentially source of hepatic injury.[7] However, the safety and efficacy of the hepatitis B vaccine in patients with RA are not known.

This study was undertaken to evaluate the humoral immune response of patients with RA to hepatitis B recombinant vaccine and to investigate the short term adverse effects and /or exacerbation of the autoimmune disease.

PATIENTS AND METHODS
Patients
Forty four consecutive patients fulfilling the American College of Rheumatology (ACR) criteria for rheumatoid arthritis[8] who gave their informed consent participated in this study, which was approved by the ethics committee for research in human beings. Subjects screening positive for hepatitis B surface antigen (HBsAg), anti-hepatitis B surface, or anti-hepatitis B core antibodies or with liver enzymes—aspartate aminotransferase and alanine aminotransferase—above the normal ranges were not enrolled. Exclusion criteria included pregnancy and a history of past vaccination allergy.

The patients, who were unaware of the study hypothesis, were allocated into one of two groups—it had been proposed that all of them would be vaccinated—those who accepted comprised the study group while the patients who declined were included in the control group. In all cases, the reason for refusing vaccination was a personal reluctance to undergo vaccination rather than an objective contraindication to it. The study group comprised 22 patients with RA who were vaccinated with three doses (each 20 µg, 1 ml) of recombinant hepatitis B vaccine (ENGERIX) intramuscularly in the deltoid region. The second and third doses were given one and six months after the first dose. The control group comprised the 22 other patients with RA who did not receive the vaccine.

Clinical assessment
A complete history and physical examination was carried out on day 0. The medical records were reviewed. Use of concomitant drugs was recorded.

Clinical assessment before, and two and seven months after immunisation included duration of morning stiffness (minutes), evaluation of daytime pain with a 10 cm visual analogue scale—where 10 represents extremely high pain and 0 no pain—and the number of tender and swollen joints.

Laboratory assessment of disease activity
Routine laboratory tests performed before vaccination, two and seven months after immunisation included complete blood cell count, serum chemistry panel, urine analysis, Westergren erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).

Humoral response to the vaccine
Antibodies to HBsAg were determined by a commercial enzyme linked immunosorbent assay (ELISA) routine test kit.

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Abbreviations: ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HBsAg, hepatitis B surface antigen; RA, rheumatoid arthritis

Table 1 Demographic and clinical characteristics of patients with RA

	Study group	Control group
Women/men (%)	17 (77)/5 (23)	18 (82)/4 (18)
Age, mean (SD)	52.9 (15.4)	51 (14.3)
Mean (SD) disease duration in year (range)	11.2 (9.4)	7.6 (7)
Number of patients RF positive (%)	16 (73)	16 (73)

Table 2 Drugs used by patients and controls at vacination and after seven months. Results are shown as No (%) unless indicated otherwise

	Study group		Controls	
Drug	Week 0	After 7 months	Week 0	After 7 months
NSAIDs	10 (45)	9 (41)	12 (55)	10 (45)
Prednisone	10 (45)	10 (45)	13 (59)	12 (55)
Mean (SD) dose (mg/day)	7.5 (3.3)	7.4 (3.2)	7.4 (3.2)	7.3 (3.3)
Hydroxychloroquine	4 (18)	3 (14)	3 (14)	3 (14)
Methotrexate	17 (77)	15 (68)	10 (45)	13 (59)
Mean (SD) dose (mg/week)	11.6 (2.6)	12.3 (2.4)	14.6	14.5
Azathioprine	2 (9)	1 (5)	2 (9)	2 (9)
IM gold	5 (23)	5 (23)	2 (9)	1 (5)
Sulfasalazine	2 (9)	1 (5)	2 (9)	1 (5)

Patients were regarded as responders if antibody titres after vaccination were greater than 10 IU/l.

Statistical analysis

Statistical analysis was carried out with the SPSS software, version 10. Repeated measurement analysis of variance was performed to compare measures of disease activity across three time periods and between groups.

Descriptive statistics, Fisher's exact test, Student's *t* test, and Mann-Whitney tests when needed were used to compare patients and controls.

RESULTS
Patients' characteristics

Table 1 shows the demographic and clinical characteristics of the patients and controls. Both groups had comparable proportions of women and were of similar mean age. Disease duration was longer in the study group. Sixteen of 22 patients were positive for rheumatoid factor in each group.

Table 2 summarises the drugs used by the patients—the greatest proportion of patients were treated with methotrexate.

Adverse effects

None of the patients reported any adverse effect after vaccination.

Disease activity

Vaccination was not associated with a significant worsening in any clinical or laboratory measure of disease. The different measurements of disease activity of the patients and controls over the study period were not statistically different. The combined p value (time×group) for each measurement was 0.76 for daytime pain, 0.1 for morning stiffness, 0.24 and 0.3 for tender and swollen joints respectively, 0.08 for CRP, and 0.12 for ESR (table 3).

Use of drugs

No significant change in the use of drugs over the seven months of follow up was noticed—the distribution and doses of drugs in the study and control groups were similar at vaccination and after seven months (table 2).

Antigen-specific response to vaccination against hepatitis B

Fifteen of 22 (68%) patients responded to vaccination with an antibody level of more than 10 IU/l after six months—the mean (SD) antibody level of the responders after six months was 302 (54) IU/l. Humoral response to hepatitis B vaccination is expected to be more than 85% in young healthy adults.[9]

Table 3 Clinical measures of disease activity in the study and control groups. Results are shown as mean (SD)

	Week 0		1 Month		7 Months		p Value*		
	Study group	Control group	Study group	Control group	Study group	Control group	Time	Group	Time×group
Daytime pain	3.25 (2.4)	3.8 (2.1)	3.1 (2.2)	4 (2.3)	2.6 (2)	3.7 (2.2)	0.18	0.14	0.76
Morning stiffness (min)	38.6 (39.2)	57.7 (59.1)	32.5 (28.6)	65.2 (68)	25.8 (26.1)	65.2 (68)	0.1	0.01	0.1
No of tender joints	4.5 (3.9)	5.9 (6.1)	4.1 (3.8)	5.2 (4.2)	3.8 (4)	5 (4.6)	0.12	0.17	0.24
No of swollen joints	2.6 (2.1)	3.36 (4)	2.2 (1.6)	2.9 (3.1)	1.7 (1.7)	2.9 (3.1)	0.16	0.1	0.3
CRP (mg/l)	1.71 (0.9)	2.5 (2.8)	1 (1)	1.7 (1.8)	1 (1.1)	2.1 (2.3)	0.1	0.08	0.08
ESR (mm/1st h)	27.2 (17.5)	38 (18.4)	27.2 (19.8)	32.8 (13.3)	28 (19.7)	32.7 (16.3)	0.28	0.15	0.12

*p Value using analysis of variance with repeated measures where "time" represents the behaviour of the groups over time, "Group" the differences between groups, and "Time×group" the difference between groups over the period of seven months.
For each of the measurements tested, no significant difference between groups was found.

Factors influencing the antibody response to hepatitis B vaccine

Lack of humoral response was significantly associated with older age (mean (SD) age 59 (10.5) in non-responders v 46.3 (17.5) in responders) and increased daytime pain at vaccination (4.8 (4.8) in non-responders v 2.2 (2.1) in responders). The humoral response was not associated with the number of tender and swollen joints at vaccination, ESR, CRP or the use and doses of drugs such as prednisone, methotrexate, azathioprine, hydroxychloroquine, intramuscular gold, and non-steroidal anti-inflammatory drugs.

DISCUSSION

Concerns about the safety and efficacy of immunising subjects with connective tissue diseases have persisted for over 50 years.[10] Indeed, descriptions of RA have been reported after tetanus toxoid administration, influenza, and recombinant hepatitis B vaccine.[3–5 11]

Immunisation with a recombinant hepatitis B vaccine has been found to be extremely efficient.[12] The side effects are usually minor, including headache, injection site pain, tiredness, fever arthalgia, usually resolving within 24–48 hours.[12] However, together with the universal use of the vaccine, serious adverse effects have been reported, including central retinal vein occlusion, uveitis, nephrotic syndrome, central nervous system demyelinisation, and others.[12] Several rheumatological manifestations have been reported after hepatitis B vaccination. Maillefert *et al* reported a series of 22 subjects who developed rheumatic disorders after hepatitis B immunisation, including RA, exacerbation of a previously non-diagnosed systemic lupus erythematosus, post-vaccinal arthritis, polyarthralgia-myalgia, and vasculitis.[13] At least 20 cases of patients satisfying the 1987 ACR criteria for the diagnosis of RA have been described.[3–5 13]

However, these sporadic reports of connective tissue disease induction should not preclude routine immunisation of patients with RA. By analogy, although a cluster of juvenile RA was seen in children born in 1963 during an epidemic of influenza A,[11] influenza vaccination of patients with RA[14] has been well tolerated.

In our study we have shown that immunisation with a recombinant hepatitis B vaccine did not induce major side effects and was not accompanied by an exacerbation of the disease. We compared different clinical and laboratory features of disease activity in a cohort of patients who were vaccinated with hepatitis vaccine with a similar group who did not receive the vaccine. The course of the disease seven months after vaccination was similar in both groups.

Overall, the study group had significant increases in mean antibody response seven months after vaccination. However, 7/22 (32%) patients did not show a significant response to the hepatitis B vaccine, though response is expected in more than 85% of young healthy adults.[12] However, the expected response to hepatitis B vaccination in older healthy patients is not well known. The lack of antibody response was correlated with older age and high daytime pain, suggesting that immunisation should preferably be given when disease activity is low. The use of immunosuppressive drugs has been found to impair antibody response to hepatitis vaccine. Impaired response to hepatitis B vaccine has been demonstrated in children receiving anticancer chemotherapy[15] and in patients with systemic lupus erythematosus treated with oral corticosteroids.[16] In our study, treatment with low dose corticosteroids, methotrexate, azathioprine, sulfasalazine, and antimalarial drugs did not affect the antibody response.

We are aware of the limitations of this study. If hepatitis B vaccination induces only a low percentage of flares, the small number of patients included in this study might have missed it. The design of the study might have failed to demonstrate a flare or an adverse effect between the visits. Likewise, a possible selection bias inherent in the study design cannot be excluded. However, this is the first study that aimed at determining the response of patients with RA to hepatitis vaccine, and these preliminary results on the safety of the hepatitis B vaccine in patients with RA are encouraging.

In conclusion, vaccination against hepatitis in this small cohort of patients with RA was safe and was immunogenic in most of them. A subgroup of patients still remains exposed to infection with hepatitis B despite immunisation. Further studies are needed to determine the long term, large scale clinical efficacy of the vaccination as well as the factors underlying the depressed response of some patients.

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