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## HEPATITIS B VACCINE IN NON-DIALYSED URAEMIC PATIENTS: PRELIMINARY RESULTS

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### Summary

The immune response to hepatitis B vaccine was prospectively evaluated in 111 uraemic non-dialysed patients with various degrees of renal insufficiency, who received three subcutaneous injections of 5 $\mu$ g HEVAC-B (R) at monthly intervals followed by a fourth injection two months later. Following the third injection, the proportion of responders was higher (9 of 13) in patients with serum creatinine  $\leq$ 400 $\mu$ mol/L than in those with more advanced renal failure (57 of 98) and their anti-HBs concentration was significantly higher (mean geometric titre: 277 versus 72mIU/ml,  $p < 0.05$  in responders, 49 versus 14mIU/ml,  $p < 0.02$  in the whole groups). Following the fourth injection, the proportion of responders increased by about 40 per cent and a further mean five-fold rise in anti-HBs was obtained. We conclude that hepatitis B vaccination in uraemic patients should be started at an early stage of renal insufficiency, using a reinforced protocol with supplementary injection(s).

### Introduction

The response to hepatitis B vaccines is impaired in uraemic patients, either already on dialysis treatment [1,2] or with end-stage renal failure [3], when compared to healthy subjects [4]. Protocols using larger doses of vaccine and/or multiple vaccine injections have been shown to improve the proportion of responders and their anti-HBs level [5]. However, even using such reinforced protocols, immune response is often lower than in healthy subjects [3,5]. As the abnormal immune response of uraemic patients probably is related to renal failure per se, one could expect a better immune response in such patients if vaccination is started at an earlier stage of renal insufficiency. Thus we prospectively studied the immune response of uraemic, non-dialysed patients with various degrees of renal insufficiency, using a reinforced vaccination schedule.

## Patients and methods

From October 1982 to December 1984, hepatitis B vaccine (HEVAC-B (R), Institut Pasteur Production), was given to 111 uraemic patients (61 male, 50 female), mean  $\pm$  2SEM, aged  $46.5 \pm 2.8$  years, mean serum creatinine  $590 \pm 32 \mu\text{mol/L}$  (range 270–1090). Underlying renal disease was glomerulonephritis ( $n=35$ ), chronic tubulointerstitial nephritis ( $n=31$ ), polycystic kidney disease ( $n=21$ ), nephroangiosclerosis ( $n=9$ ), or other kidney diseases ( $n=12$ ).

Patients received three standard doses of  $5 \mu\text{g}$  each at one month intervals, followed by a fourth vaccine injection (V4) two months later which, until the end of 1983, was given to patients whose anti-HBs titre was lower than 50mIU/ml following the third injection (V3) and after January 1984, was routinely given, irrespective of the anti-HBs after V3. By the end of December 1984, 51 of the 111 patients had received V4 and had subsequent anti-HBs titres; 16 others were to have it in the next months; 44 did not receive V4 (20 started dialysis, 2 died and 22 had anti-HBs titres above 50mIU/ml after V3).

Anti-HBs were screened and titrated using radioimmunoassay (AUSAB (R), Abbott Laboratories) one month following V3 and V4, and were expressed as mIU/ml. Results are given as arithmetic means ( $\pm$  2SEM) and as geometric mean titre (GMT). Student's 't' test and  $\chi^2$  test were used for statistical comparisons.

## Results

### *Immune response following the third injection*

Of the 111 patients, 74 (66%) seroconverted after V3, of whom 66 (60%) defined as responders developed an anti-HBs titre  $\geq 10$ mIU/ml (including 42 high responders defined by an anti-HBs titre  $\geq 50$ mIU/ml), and eight (6%) weak responders had an anti-HBs titre of 3 to 9mIU/ml; 25 (34%) were non-responders. In the 66 responders, the mean arithmetic anti-HBs titre was  $219 \pm 86$ mIU/ml and GMT was 87mIU/ml.

The proportion of responders was significantly greater in patients under 40 years (39 of 40, or 85%) than in those over 40 years when starting vaccination (32 of 71, or 45%,  $p < 0.001$ ), but their mean anti-HBs titre was not significantly different ( $209 \pm 93$  versus  $230 \pm 147$ mIU/ml, NS). The proportion of responders was not different between males (35 of 61, or 57%) and females (31 of 50, or 62%, NS) but the mean anti-HBs titre was slightly higher in females ( $240 \pm 118$  versus  $201 \pm 122$ mIU/ml, NS). The proportion of responders did not differ according to the underlying renal disease (25 of 35 in glomerulonephritis, 22 of 34 in interstitial nephritis, 15 of 21 in polycystic disease, 5 of 9 in vascular disease group).

Immune response was significantly better in the group of 13 patients having moderate renal failure (serum creatinine  $\leq 400 \mu\text{mol/L}$ , mean  $323 \pm 28 \mu\text{mol/L}$ ) than in the group of 98 patients having more advanced renal failure (serum creatinine  $> 400 \mu\text{mol/L}$ , mean  $625 \pm 30 \mu\text{mol/L}$ ) at start of vaccination, although sex distribution and age did not differ between the two groups (Table I). The

TABLE I. Immune response to three doses of hepatitis B vaccine in patients with moderate renal failure (serum creatinine  $\leq 400\mu\text{mol/L}$ ) compared with patients with advanced renal failure (values expressed as mean  $\pm$  2SEM)

Characteristics	Serum creatinine ( $\mu\text{mol/L}$ )		p value
	$\leq 400$	$> 400$	
Number of patients	13	98	
Male/female ratio	6/7	55/43	NS
Age	46.6 $\pm$ 5.4	46.5 $\pm$ 1.4	NS
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Responders ( $\geq 10\text{mIU/ml}$ )	9 (69%)	57 (58%)	NS
arithmetic titre	431 $\pm$ 256	186 $\pm$ 88	p<0.05
GMT	277	72	
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Whole group	13	98	
arithmetic titre	298 $\pm$ 209	108 $\pm$ 54	p<0.02
GMT	49	14	

proportion of responders was slightly greater in patients with serum creatinine  $\leq 400\mu\text{mol/L}$ , but their mean anti-HBs titre was significantly higher than in patients with advanced renal failure ( $p < 0.05$ ). The same difference was true for the two groups as a whole ( $p < 0.02$ ) (Table I).

#### *Immune response following the fourth injection*

The immune response was studied in the 51 patients (26 male, 25 female) who received V4. Their initial characteristics (age  $50.2 \pm 3.8$  years, serum creatinine  $573 \pm 39\mu\text{mol/L}$ ) and the distribution of primary renal disease did not differ from that observed in the whole series. Of the 51 patients, 22 (43%) responded after V3, including 12 high responders. Following V4, 32 of 51 (63%) had an anti-HBs titre  $\geq 10\text{mIU/ml}$  (including 25 high responders), whereas the cumulated proportion of non and weak responders decreased from 57 per cent to 37 per cent. Following V4, the 25 non responders became 15 non responders, three weak responders, three responders and four high responders; the four weak responders became one weak responder, one responder and two high responders; the 12 responders improved to four responders and eight high responders, and the 10 high responders remained high responders. Overall, the rate of seroconversion rose from 51 per cent to 71 per cent after V4.

Moreover, the fourth injection significantly improved the mean anti-HBs titre in responders (with a five-fold increase from  $156 \pm 127$  to  $736 \pm 477\text{mIU/ml}$ ,  $p < 0.05$ ). A five-fold increase (from  $68 \pm 59$  to  $383 \pm 244\text{mIU/ml}$ ,  $p < 0.02$ ) was similarly observed following V4 in the whole group of 51 patients.

## Discussion

The present data clearly show that patients with advanced chronic renal failure have an impaired immune response to hepatitis B vaccination, as observed in uraemic patients treated by chronic haemodialysis receiving the same vaccine [1]. However, even with reinforced protocols, this immune response of dialysed and end-stage uraemic patients is lower than in healthy subjects [5]. In view of the high risk of contamination in dialysis centres and of the rapid decrease in anti-HBs while on dialysis treatment [2,6], all efforts should be made to improve the immune response of uraemic patients before they reach end-stage renal failure.

Our data indicate that the immune response in uraemic patients having mild or moderate renal failure (serum creatinine  $\leq 400\mu\text{mol/L}$ ) is markedly better than in patients having advanced renal failure when starting vaccination, both with respect to the proportion of responders and to the anti-HBs titres. These observations agree with the conclusion of Bommer et al, who reported a higher rate of seroconversion and a higher median anti-HBs level in patients with a serum creatinine not in excess of  $3.5\text{mg/dl}$  [7] and with those of Legrain et al [8], using HEVAC B vaccine. Moreover, in our patients, a fourth injection performed two months after the first three doses markedly improved the immune response, as observed by Goudeau et al [9] with a 40 per cent supplementary seroconversion and a mean five-fold increase in the anti-HBs level.

Thus, we conclude that hepatitis B vaccination in uraemic patients should be started early, before serum creatinine concentration exceeds  $400\mu\text{mol/L}$  (or creatinine clearance is less than  $25\text{ml/min}$ ), using reinforced protocols with supplementary injection(s).

## References

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