Immunisation against varicella in end stage and pre-end stage renal failure

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Abstract

Objectives—To investigate the seroconversion rate and duration of persistence of protective antibody titres after varicella immunisation in children with renal failure.

Design—32 children (25 end stage and 7 pre-end stage renal failure) were immunised using 2×2000 plaque forming unit doses of varicella vaccine 3 months apart. Varicella antibody titres were measured by enzyme linked immunosorbent assay.

Results—All children initially seroconverted after immunisation. At a mean follow up of 20.3 months, 23 of 28 had protective antibody titres, 4 children having died of unrelated causes. Two children required a third booster dose. 11 children underwent renal transplantation; 10 had protective titres at the time of transplantation and, at a mean of 23.4 months after immunisation, 6 currently have protective titres. Minor side effects occurred after 11 vaccine doses in 9 children. No child developed varicella, despite 10 clear episodes of exposure to the wild-type virus.

Conclusions—Varicella immunisation in children with end stage and pre-end stage renal failure results in a high rate of seroconversion and persistence of protective antibody titres. More widespread use of the vaccine before renal transplantation is recommended.

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Keywords: immunisation; varicella; end stage kidney failure; renal transplantation

Varicella in the immunosuppressed renal transplant recipient is a more serious infection than that observed in normal children, with considerable morbidity and a mortality rate of up to 25%.^{1–3} Affected children require admission to hospital and the use of high dose antiviral agents, which can impair allograft function. The development of varicella in those with no naturally acquired immunity can be prevented by the administration of zoster immune globulin soon after exposure to varicella zoster virus (VZV) where this is recognised. Such treatment is expensive, involves intramuscular injection, and exposes the child to the risk of blood borne virus infection. Furthermore, passively acquired immunity is short lived, with further doses being required after subsequent exposure, and zoster immune globulin is in increasingly short supply. Although controversy surrounds universal childhood vaccina-

tion against VZV, there is support for the immunisation of high risk populations.^{4 5}

Current guidelines recommend that all children with pre-end stage and end stage renal failure receive all routine childhood immunisations and additional immunisations against hepatitis B, influenza, and *Streptococcus pneumoniae*. All necessary live immunisations should be administered before entry on to the transplantation waiting list because they are contraindicated once immunosuppressive treatment has been commenced.⁶ However, the presence of end stage renal failure is reported to reduce the immunological response to certain vaccines, including hepatitis B vaccine.⁷

The addition of live attenuated varicella vaccine to the above list to provide protective immunity after transplantation would be a logical step, although the subject has received little attention to date. A retrospective review of 212 children, who received a single 1000 plaque forming unit (PFU) dose of vaccine, reported an 87% seroconversion rate. Only 62% of children had protective antibody titres one year after immunisation, which fell to 52% at the time of transplantation. Despite the seemingly poor persistence of circulating antibody titres using this immunisation regimen, the incidence of varicella in the transplanted population fell from 45% to 12% after the introduction of immunisation.⁸ In a further study of 17 patients with end stage renal failure and 17 with functioning transplants who were also immunised with a single 1000 PFU dose of vaccine, 85% developed antibodies within the first six months, and 76% of the end stage patients had protective antibody titres at one year. Three children acquired varicella two to four years after successful immunisation, although in all cases the disease was in an attenuated form.⁹ Neither study reported data regarding exposure to wild-type VZV, and vaccine response rates were inferior to those reported elsewhere in healthy children.^{10 11}

We designed our study to determine whether immunisation of children with end stage and pre-end stage renal failure using a higher dose live attenuated varicella vaccine (two doses of 2000 PFU) resulted in an improved duration of immunity, and to collect prospective data regarding exposure to wild-type virus after immunisation. Our specific aims were: (1) to determine the seroconversion rate, duration of persistence of protective antibody titres, and incidence of side effects after immunisation; and (2) to determine the protective efficacy of this vaccine after seroconversion in those children subsequently exposed to VZV.

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Table 1 Primary renal diagnosis in study participants

Diagnosis	n
Renal dysplasia/hypoplasia	10
Congenital nephrotic syndrome	5
Nephronophthisis	3
Posterior urethral valves	3
Prune belly syndrome	2
Other urological abnormalities	2
Bardet Biedel syndrome	1
Focal segmental glomerulosclerosis	1
Unspecified glomerulonephritis	1
Haemolytic uraemic syndrome	1
Interstitial nephritis	1
Reflux nephropathy	1
Townes Buck syndrome	1

Methods

The study group consisted of children with end stage renal failure on dialysis and pre-end stage renal failure (predicted glomerular filtration rate, $< 20 \text{ ml/min/1.73 m}^2$ calculated using the Schwartz formula¹²) who had no previous history of varicella infection and were VZV IgG antibody negative by enzyme linked immunosorbent assay (ELISA). Children receiving immunosuppressive treatment were excluded from our study. Children were immunised using $2 \times 2000 \text{ PFU}$ doses of live attenuated varicella vaccine (Oka strain) (Pasteur Merieux MSD, Maidenhead, Berks UK) given three months apart. Serum VZV IgG antibody titres were measured by ELISA (Diamedix, Miami, USA), monthly for the first six months after immunisation and three monthly thereafter. Immunity to VZV was defined as a circulating antibody titre of 20 eu/ml or greater.¹³ At the time of immunisation, parents were issued with booklets to record any side effects and to document subsequent episodes of exposure to wild-type VZV. Where such exposure was recognised, the antibody titre was repeated and regular telephone contact was made with the family over the next 21 days. Where infection was suspected, children were reviewed by a principal investigator. Children awaiting renal transplantation were removed from the transplant waiting list for a six week period after each vaccine dose.

Fully informed consent was obtained from parents before entry into the study, for which ethical approval was granted by the Salford and Trafford, Royal Liverpool Children's Hospital, and St James's University Hospital local research ethics committees.

Results

A total of 32 children (20 boys, 12 girls) in the three participating centres were found to meet the study entry criteria, and all were entered into our study at a mean (SD) age at the time of first immunisation of $3.8 (2.9)$ years. Twenty

five had end stage renal failure (19 on peritoneal dialysis and six on haemodialysis) and seven had pre-end stage renal failure; the range of primary renal pathologies is shown in table 1. Thirty one children received both vaccine doses, and mean (SD) follow up from immunisation to date or to death was $19.1 (5.5)$ months. Four children have died, three after the elective withdrawal of end stage renal failure treatment (one between the first and second immunisations) and one after complications of transplantation. All 28 surviving children have completed at least one year of follow up after immunisation.

All children initially seroconverted after immunisation, and at a mean (SD) follow up of $20.3 (4.3)$ months, 23 of the 28 survivors had protective antibody titres (mean (SD) antibody titre, $71.8 (47.5) \text{ eu/ml}$). All four children who died had protective titres at the time of their death. Two children, both with end stage renal failure (one on peritoneal dialysis and one on haemodialysis) have required a third booster dose of vaccine, having initially seroconverted after immunisation but subsequently lost their protective antibody titre. After re-immunisation, both had protective antibody titres at 12 and eight months after their third vaccination.

Eleven children have undergone renal transplantation, of which 10 are currently alive. Seven are receiving cyclosporin A, azathioprine, and prednisolone, and three are receiving tacrolimus, azathioprine, and prednisolone immunosuppressive regimens. No child has required monoclonal or polyclonal antilymphocyte antibodies as induction or antirejection treatment. These 10 children have now been followed for a mean (SD) of $23.4 (3.9)$ months after immunisation and $14.2 (5.4)$ months after transplantation, and six currently have protective antibody titres. Ten of the 11 had protective titres at the time of transplantation. There have been no graft losses in this group, and the acute rejection rate of 30% is similar to that reported in most current paediatric series.¹⁴

A total of five children do not currently have protective antibody titres. Four of these have undergone transplantation, thus precluding the administration of a third booster dose, and the fifth is currently awaiting a booster dose. Of these four transplanted children, three had protective antibody titres at the time of transplantation, these being lost at two, 12, and 13 months after transplantation. Overall, the characteristics of these five children did not

Table 2 Characteristics of the five children without current protective antibody titres

Age at immunisation	Sex	Diagnosis	Time post-immunisation of loss of protective antibody titre	Current status
1 year 5 months	F	Congenital nephrotic syndrome (nephrectomised)	4 months	Functioning transplant
4 years 0 months	F	Renal dysplasia	1 year 10 months	Functioning transplant
2 years 1 month	M	Renal dysplasia	2 years 0 months	Functioning transplant
6 years 9 months	M	Posterior urethral valves	2 years 0 months	Functioning transplant
2 years 11 months	M	Renal dysplasia	9 months	Pre-end stage renal failure*

*Currently awaiting booster dose.

differ from the study population as a whole (table 2).

No major side effects were reported by parents after immunisation, although minor side effects that did not result in medical consultation occurred after 11 vaccine doses in nine children (fever, four; inflammation at immunisation site, seven). No child has developed zoster as a consequence of vaccination.

No child developed varicella, despite 10 clear episodes of exposure to wild-type VZV in a total of seven children, five before transplantation and five after transplantation. All children had satisfactory circulating antibody titres at the time of these contacts and remained clinically well.

Discussion

We have shown that immunisation with 2×2000 PFU doses of live attenuated varicella vaccine results in high levels of seroconversion and persistence of protective antibody titres in children with end stage and pre-end stage renal failure. These results are highly favourable compared with previous studies investigating varicella immunisation in children with renal failure, which reported 62%⁸ and 76%⁹ of children as having protective antibody titres at one year after immunisation. This might be because of the use of a higher vaccine dose and a two dose immunisation schedule. Recent evidence suggests that low dose vaccines are a risk factor for breakthrough varicella infection.¹⁵

Only two children required a third booster dose of vaccine after the loss of an initially protective antibody titre (a third is currently awaiting re-immunisation), and in both instances protective antibody titres were once again induced. Booster doses were only administered where children had not undergone transplantation. Current UK recommendations state that live vaccines should not be given to immunosuppressed solid organ transplant recipients,⁶ although there are reports of the use of varicella vaccine in this population.⁹ Immunisation before transplantation resulted in 10 of 11 children having protective antibody titres at the time of transplantation, and of the three children who subsequently lost their protective titres, two had immunity for the duration of the first 12 months after engraftment, when immunosuppressive treatment is most intense. We could deduce no obvious risk factors for the loss of protective antibody titres; no child had heavy proteinuria with consequent high urinary IgG losses. Although children with subprotective antibody titres were defined as being non-immune for the purposes of our study, cell mediated immune mechanisms might well have conferred satisfactory immunity.

There were no documented episodes of varicella infection after immunisation, despite a number of well documented episodes of exposure to wild-type VZV. The incidence of side effects was low, in keeping with other studies of this vaccine.

There are, at present, no UK or USA guidelines for the use of varicella vaccine in end stage

and pre-end stage renal failure, although over 70% of North American nephrology centres recently surveyed stated that they recommended its use.¹⁶ The results of our study allow us to make a preliminary recommendation for the use of the vaccine in this population of children, using a 2×2000 PFU dose regimen before renal transplantation. Concentrations of anti-VZV IgG should be monitored on a regular basis after immunisation, and where loss of a previously protective antibody titre occurs, we recommend the use of a third booster dose, although we have not investigated this in children who have undergone transplantation in the intervening period. Larger numbers and a longer duration of follow up are clearly necessary before a more definite statement can be made, and further data need to be collected regarding the use of the vaccine in non-immune patients who have already undergone transplantation. The vaccine also warrants further investigation in other at risk groups, including children with other end stage organ diseases likely to require solid organ transplantation, and those on long term continuous or intermittent immunosuppressive treatment for disorders such as childhood nephrotic syndrome.

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