


REGULAR ARTICLE

Long-term study showed that vaccination protected paediatric renal transplant recipients from life-threatening varicella zoster virus

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ABSTRACT

Aim: Renal transplant patients are particularly susceptible to highly contagious diseases due to their reduced immunity. We studied transplant recipients to gauge their varicella zoster virus (VZV) serology status over time and the outcome of any VZV infections.

Method: This retrospective study comprised 85 children who underwent renal transplants in Gothenburg, Sweden, from 1986 to 2014, at a mean age of eight (1–18) years. The children's medical records were reviewed and 47 had the VZV infection pre-transplant and 38 had been vaccinated pre-transplant. Clinical outcomes were available for 85 children and serology results for 72.

Results: At transplantation, the VZV seropositivity rate was 50% in the vaccination group and 94% in the infection group and the antibody titres were significantly lower in the vaccination group ($p = 0.031$). During the median follow-up period of five years post-transplant, 28% of the vaccinated children and 97% of the infection group remained seropositive and the varicella infection affected eight children: one in the infection group and seven in the vaccination group. The herpes zoster was observed in two children in the infection group.

Conclusion: This study demonstrated that VZV vaccination protected from symptomatic infections to a lesser extent than natural infection, but provided effective protection from life-threatening disease.

INTRODUCTION

The varicella zoster virus (VZV) infection is common in children and immunosuppressed paediatric patients risk contracting this highly contagious disease. Both the primary infection, varicella, and the reactivated infection, herpes zoster, can be severe and may cause significant morbidity and mortality in immunocompromised patients who lack protective immunity (1,2). Feldhoff et al. studied renal transplant recipients in 1968–1979, before antiviral prophylaxis or treatment was available (3). Of the 19 patients who developed varicella, eight developed severe disease and one died (3). In another report, a series of 83 VZV-naïve children with renal grafts were observed in 1979–1991: four of the eight children with varicella developed

visceral disease and two of them died, despite antiviral treatment (4). With the introduction of acyclovir treatment against the VZV infection, morbidity and mortality have been successfully reduced (5–8). In spite of this, the VZV infection is a real threat to non-immune immunocompromised individuals and post-exposure prophylaxis using

Abbreviations

CMV, Cytomegalovirus; D+, D–, Donor positive, donor negative; ELISA, Enzyme-linked immunosorbent assay; IQR, Interquartile range; R+, R–, Recipient positive, recipient negative; VZV, Varicella zoster virus.

Key notes

- We studied 85 renal transplant patients for varicella zoster virus (VZV) immunity over time and the outcome of VZV infections.
- At transplantation, significantly more patients were seropositive after the varicella infection than after vaccination and vaccinated patients then lost their seropositivity to a greater extent than previously infected individuals.
- Varicella vaccination protected from symptomatic VZV disease less than natural infection, but provided effective protection from life-threatening disease.

antiviral treatment, and in some cases, human varicella zoster immunoglobulin is also necessary.

A live attenuated varicella vaccine, Oka, was developed in Japan about 40 years ago (9) and this was originally used to prevent the primary VZV infection in immunocompetent individuals. It was shown to be safe, immunogenic and efficacious after a single dose in healthy children (10,11). White et al. reported a 96% serological response after vaccination with one dose and an incidence of varicella after household exposure of 12% vs. 87% in historically non-immunised children (11). Later studies demonstrated that a two-dose regimen was significantly more effective than a single injection in preventing the varicella infection (12,13). These days, the varicella vaccination is widely used and recommended for the routine vaccination of children in several countries, including the United States (14,15). Finland started immunisation in 2017, but in the other Nordic countries, including Sweden, the varicella vaccination is not offered.

Patients with end-stage renal disease have a reduced response to vaccination because of the general suppression of the immune system associated with uraemia, which may be due to disturbances in T lymphocytes and antigen-presenting cells. In 1985, Broyer et al. presented encouraging results with active immunisation against varicella in seronegative children considered for renal transplants (16). During the following two decades, non-randomised studies in patients with end-stage renal disease demonstrated that the Oka vaccine was safe prior to transplant (17–20). However, patients with end-stage renal disease exhibited lower seroconversion rates to a single-dose varicella vaccine than healthy children: 85–88% vs. 99% (17–19,21,22). Prospective, multicentre studies that evaluated antibody levels in children with end-stage renal disease after a two-dose regimen of varicella vaccine revealed that 98–100% of the patients seroconverted after the second dose (18,19). However, few infants were included in these studies and this means that the seroconversion rates in infants and toddlers with end-stage renal disease after either one or two doses of the varicella vaccine are less known. It has, therefore, been suggested that two doses should be given prior to transplantation, with a minimum interval of four to six weeks (23, 24).

When more countries introduce routine varicella vaccinations for children, the majority of children undergoing renal transplants will be vaccinated. VZV serology status over time has not been investigated to any extent in renal transplant patients using modern immunosuppression. That is why this study aimed at comparing VZV immunity and infection outcomes among children who had received varicella vaccination with those who had experienced varicella infections during the pre-transplant period.

The aims of the study were (i) to assess VZV serology in paediatric renal transplant recipients at the time of their transplant, (ii) to follow antibody levels over time in children with a pre-transplant history of varicella infection or vaccination and (iii) to determine the occurrence and

describe the clinical outcome of varicella and herpes zoster after transplants in the two cohorts.

PATIENTS AND METHODS

Patients and study design

This retrospective study involved 90 paediatric patients who were consecutively transplanted with renal grafts at Queen Silvia Children's Hospital, Sahlgrenska University Hospital in Gothenburg, Sweden, between 1986 and 2014. We excluded five patients from the entire study: one patient lacked a proven history of varicella infection or vaccination prior to their transplant, and the VZV serostatus was missing from four patients before their transplant (Fig. 1). A further 13 patients lacked serology data post-transplant and therefore excluded from the serology follow-up, but were still followed for clinical outcomes. A total of 85 were evaluated for clinical outcome, and of these, 72 children were also evaluated for serology. The patients were followed until May 2015. The investigation was approved by the Ethics Committee for Medical Research at Gothenburg University (number 549-13).

The children were divided into two groups: those who presented a history of varicella infection and those who were vaccinated before transplantation. We found that 38 children had been vaccinated with the live attenuated Oka strain of VZV vaccine at different time points before transplantation. Prior to 2005, the 23 VZV seronegative patients were given either one or two doses of varicella vaccine, whereas the 15 patients transplanted from 2005 and onwards received two doses of vaccine at least six weeks apart.

Using a clinical chart review, we obtained results from serological analyses before and at various time points after transplantation, along with any symptoms of clinical VZV infection and survival data. The patients were excluded from the follow-up of VZV serology if they developed the VZV infection, had another transplant, died or were lost to follow-up.

The diagnosis of symptomatic VZV infection after transplantation was based on typical clinical signs. The asymptomatic reactivation of VZV was determined as a fourfold or greater increase in VZV serology titre without any described symptoms or treatment for VZV in the patient's chart.

Immunosuppression

The initial immunosuppressive treatment after transplantation is summarised in Table 1. It varied during the study period according to recommended guidelines and protocols. The 34 patients transplanted between 1986 and 1998 received graft rejection prophylaxis with cyclosporine, azathioprine and corticosteroids. The 12 recipients transplanted between 1999 and 2004 received prophylaxis with tacrolimus, azathioprine and corticosteroids, while the 22 recipients transplanted between 2005 and 2010 were given tacrolimus, mycophenolate mofetil and corticosteroids. The final 17 patients transplanted from 2011 to 2015 received a

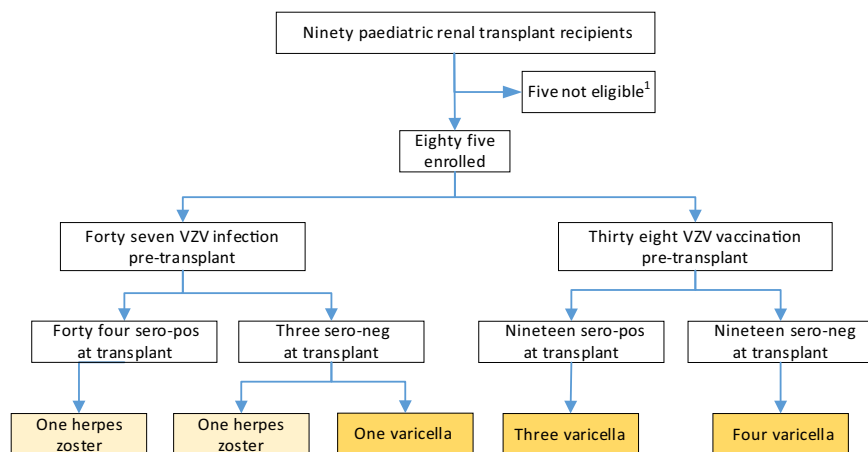


Figure 1 Enrolment and clinical follow-up showing the pre-transplant serostatus of renal transplant recipients and the development of VZV disease during the follow-up period. ¹Five patients were excluded from the study: one lacked a proven history of varicella infection or vaccination pre-transplant and four patients lacked serology status pre-transplant.

regimen that included basiliximab, tacrolimus, mycophenolate mofetil and corticosteroids.

Antiviral prophylaxis

Antiviral prophylaxis against herpes viruses was routinely given to patients at high risk of cytomegalovirus (CMV) infection, for example those who were donor positive (D+), recipient negative (R−) for CMV immunoglobulin

G (IgG) antibodies before their transplant, donor negative (D−), recipient positive (R+) and D+R+ patients. The 23 D+R− patients were given prophylaxis with aciclovir (1992–1997), ganciclovir (1998–2005) or valganciclovir (2005–2015) that started seven days post-transplantation and continued for at least six months after transplantation. The 19 D+R+ and D−R+ patients received this for at least three months. The distribution of antiviral prophylaxis in the two groups of patients is shown in Table 1.

Table 1 Patient characteristics

Characteristics	Varicella infection pre-transplant (n = 47)	Varicella vaccination pre-transplant (n = 38)
Age at renal transplantation; median; range (years)	12, 2–18	4, 1–15
Male gender	25 (53%)	29 (76%)
Diagnosis		
Congenital nephropathy and structural abnormalities	17 (36%)	22 (58%)
Hereditary renal disorders	11 (23%)	11 (29%)
Glomerulopathies and acquired diseases	18 (38%)	5 (13%)
Unknown	1 (2%)	0 (0%)
Living donor	29 (62%)	33 (87%)
Antiviral prophylaxis for three months	13 (28%)	6 (16%)
Antiviral prophylaxis for six months	13 (28%)	10 (26%)
Second renal transplantation	14 (30%)	8 (21%)
Initial immunosuppressive regimen included		
Azathioprine	23 (49%)	23 (61%)
Basiliximab	10 (21%)	7 (18%)
Corticosteroids	47 (100%)	38 (100%)
Cyclosporine	18 (38%)	16 (42%)
Mycophenolate mofetil	24 (51%)	15 (39%)
Tacrolimus	29 (62%)	22 (58%)

Determination of VZV antibodies

An enzyme-linked immunosorbent assay (ELISA) was used to detect VZV antibodies from the IgG class using whole virus antigen (1986–2011) or recombinant VZV glycoprotein E antigen (2012–2015) for coating (25,26). The sera were diluted in two steps before analyses. The cut-off level was set as an optical density value of a negative serum control diluted 1:200 plus 0.200 optical density units. A VZV IgG antibody titre of at least 200 was considered seropositive, indicating prior VZV antigen exposure (25). In addition, in specimens with a VZV IgG titre of 200 against the whole virus antigen, immunofluorescence analyses were carried out and a titre of eight was regarded as positive (26). Changes in antibody titres were considered significant when a fourfold or greater titre increase or decrease was seen. The coefficient of variation for ELISA using the whole virus antigen was 14% between tests. The coefficient of variation for glycoprotein ELISA was 15% between variation and 6% within variation.

In this study, we included serum samples analysed at the various time points. Sera taken one year pre-transplant to seven days post-transplant were regarded as day zero, and 79/85 individuals had serum samples taken within this time interval. In the other six cases, the sera were sampled more than one year before their transplant, with a median time of 549 days. During the serological follow-up, we accepted

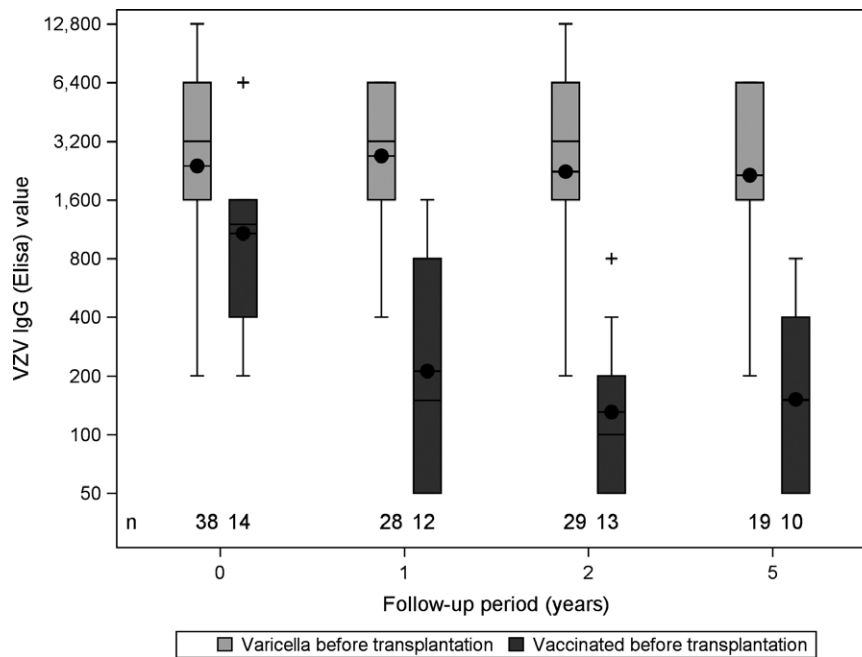


Figure 2 VZV antibody levels over time in renal transplant patients who were seropositive at transplant after a previous varicella infection or vaccination. Distribution of VZV IgG titres measured at zero, one, two and five years post-transplant. The VZV IgG median (—) and geometrical mean (●) titres are marked for all groups. + indicates outliers. Patients were excluded from serological follow-up at symptomatic and asymptomatic VZV infections, loss to follow-up, retransplantation or death. n = Number of individuals analysed at each time point. Accepted time frames at the different time points for collection of serum: zero from –365 days pre-transplant to seven days post-transplant (six individuals had sera sampled prior to one year before transplant, at a median of 549 days pre-transplant); one year from 0.5 to 1.5 years; two years from 1.5 to 3.5 years; and five years from 3.5 to 7.5 years.

analyses of sera that have been carried out one, two and five years after the patients’ transplants (Fig. 2).

Statistical methods

Fisher’s exact test was used to compare the presence of VZV antibodies between the two groups, namely VZV infection pre-transplant and vaccination pre-transplant. The Mann-Whitney U-test was used to compare antibody levels between the two cohorts and for comparisons between groups for continuous variables. Wilcoxon’s signed-rank test was used for comparisons within the groups in Figure 2. The time-to-event variables – death, VZV IgG titre <200 or VZV disease – were shown graphically using the Kaplan-Meier technique for survival data in the two groups of patients, who were infected or vaccinated before their transplant. The comparison of these variables between the two groups was performed using the log-rank test. Cox proportional hazards univariate and multivariate models, adjusted for age, were used to produce hazard ratios, associated 95% confidence intervals (95% CI) and p-values. Interactions between the group variables and age were also investigated, but they were not found for any of the studied outcomes. The assumption of proportional hazards was checked and found to be correct. All tests were two-tailed and conducted at a significance level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics

The characteristics of the 85 paediatric renal transplant recipients are shown in Table 1. Before their transplants, 47 children had the varicella infection and 38 were vaccinated. The vaccinated children were significantly younger (p = 0.0001) than those who had been infected. Renal failures, leading to transplantation, were caused by more than 20 different diagnoses, which were grouped into four categories, as shown in Table 1. The vaccinated children had a higher prevalence of congenital nephropathies and structural abnormalities, whereas the children with previous varicella infection were more likely to suffer from glomerulopathies and acquired diseases. Prior to transplantation, 65% of the patients were on dialysis therapy and they were equally split between the infected and vaccinated groups. Plasma exchange treatment was given to one patient in each group pre-transplant. Immunosuppressive treatment was given to 14 patients: four in the vaccination group and 10 in the infection group. This was frequently many years prior to transplant and in no cases was the treatment given less than a year before transplantation. The initial immunosuppressive treatment after transplantation was similar in the two cohorts of patients (Table 1). Of the 85 patients, 35 (41%) developed graft rejections and 22 (26%) patients underwent a retransplantation at a median time of six, interquartile range (IQR) of three years to 12 years after the initial transplant for those with previous

varicella infection and eight (IQR: 4–13) years for those who were vaccinated. A total of six patients died during the clinical follow-up: two patients belonged to the infection group and four to the vaccination group ($p = 0.019$). No patient died due to VZV disease.

VZV antibody responses

The 85 patients were divided into groups, based on their pre-transplant VZV history combined with their serology status (Fig. 1). All the children had been routinely tested for the presence of serum IgG antibodies against VZV before transplantation and then at various time points for a median time of five (range: 0–21) years post-transplant.

At transplantation (day zero), the frequency of VZV seropositivity was significantly higher in patients with a history of the varicella infection (44/47, 94%) than in those who had been vaccinated pre-transplant (19/38, 50%, $p < 0.0001$). In the seropositive patients, the geometric mean antibody titre was significantly higher in the infection than in the vaccination group (2390 vs. 1076, $p = 0.030$).

Due to the lack of serum samples after transplantation, seven patients in the infection group and six in the vaccination group were excluded from the serological follow-up. Of the 72 children who were followed serologically until censoring at VZV infection, loss to follow-up, retransplantation or death, 52 were seropositive at day zero. Of these, 38 of them had a history of varicella and 14 had been vaccinated. The patients with a history of varicella infection had significantly higher VZV antibody titres than those who had been vaccinated, when they were studied one, two and five years after transplantation ($p < 0.0001$;

Fig. 2). Only one of the 38 children who were seropositive at day zero after a previous varicella infection became seronegative, but 14 (37%) of them had a fourfold or greater reduction in antibody levels during the follow-up period. In contrast, 10 (71%) of the 14 vaccinated patients who were seropositive at day zero became seronegative at a median time of 1.7 (IQR: 1–4) years after transplantation. The remaining four vaccinated patients stayed seropositive throughout follow-up, but one individual had a fourfold reduction in antibody levels. Thus, after up to five years' follow-up of the seropositive individuals, significantly more patients in the infection group (97%) remained seropositive than those in the vaccination group (28%, $p < 0.0001$) (Fig. 3). Moreover, the probability of not experiencing VZV disease was significantly higher in the group with previous varicella infection in comparison with those who had been vaccinated ($p = 0.012$; Fig. 4). However, the difference in hazard ratio between the groups was no longer significant when adjusted for age.

During the follow-up period, five patients had a significant increase in VZV antibody titres without clinical symptoms. No data regarding an infectious episode or antiviral treatment were noted in these patients' charts. These patients belonged to the vaccination group: two were seropositive and three were seronegative at day zero and their asymptomatic infections were detected two to eight years after transplantation.

Varicella and herpes zoster after transplantation

Of the 85 studied patients, 10 developed symptomatic VZV disease during a median follow-up period of 10 (range: 0.5–

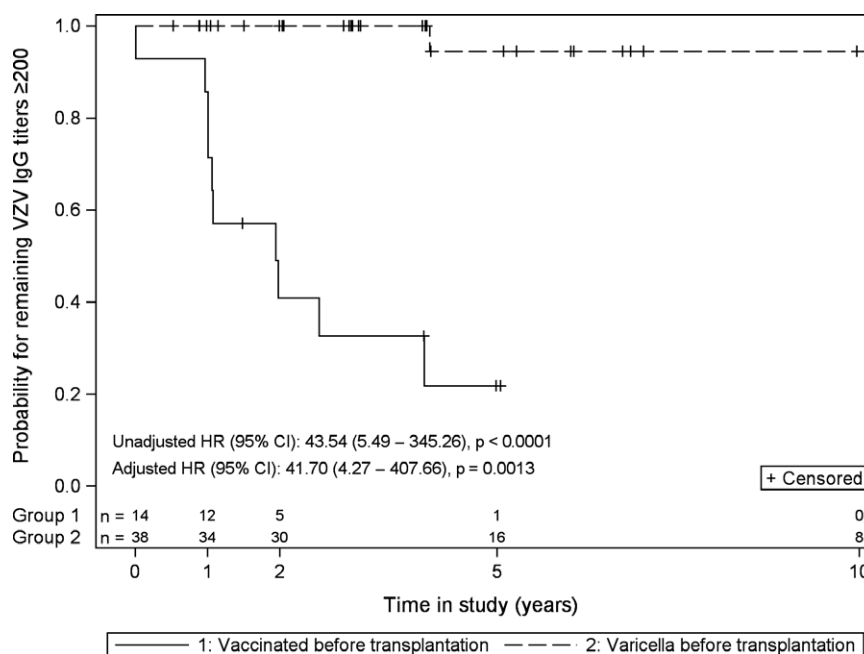


Figure 3 Persistence of a VZV antibody level of ≥ 200 after renal transplantation. Only seropositive individuals were included at the start. Censored at retransplantation, symptomatic or asymptomatic VZV infections, death and loss to follow-up. n = Number of patients at risk of becoming seronegative at each time point; HR = Hazard ratio; CI = Confidence interval.

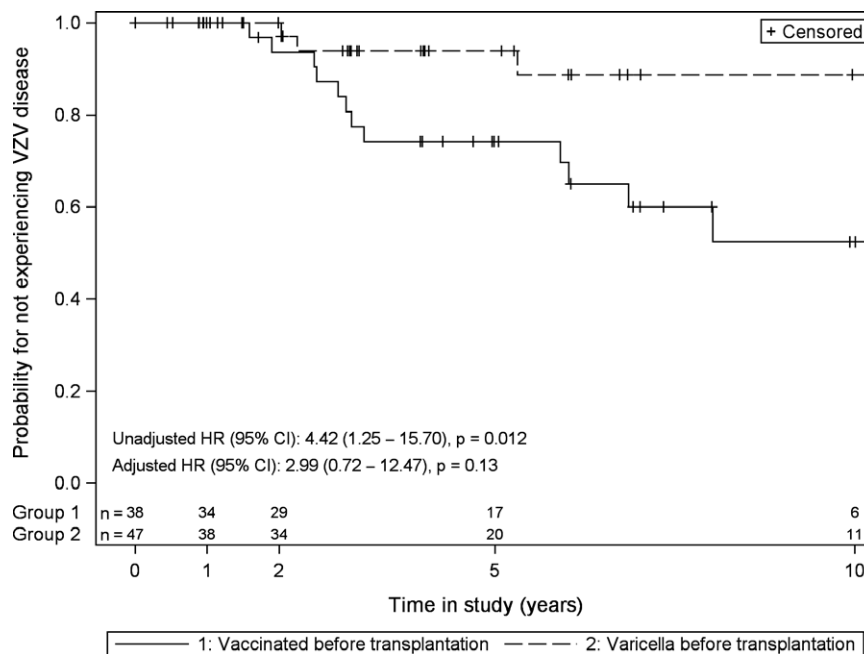


Figure 4 Probability of not experiencing VZV disease after renal transplantation. All individuals were included at the start. Censored at retransplantation, death and loss to follow-up. n = Number of patients analysed at each time point; HR = Hazard ratio; CI = Confidence interval.

28) years post-transplant (Fig. 1). Clinical varicella infection affected eight patients: seven had been vaccinated before transplantation—four while they were on a dialysis regimen—and one had a history of varicella pre-transplant. Of these eight patients, five were already seronegative at day zero and the other three became seronegative post-transplant before developing varicella. The time interval between transplants and the varicella infection was two years in four patients, three years in two patients and four and seven years in the other two patients. None of the patients had graft failure or were on post-transplant dialysis therapy at the time of the varicella infection or before. All eight patients presented with mild varicella infection, with no fever or low-grade fever, a moderate amount of skin lesions and no other complications.

Two patients experienced herpes zoster during follow-up and they both belonged to the pre-transplant varicella infection group. One of the patients had an antibody titre of 1600 but still developed the herpes zoster during the first year after transplantation. The other patient who experienced herpes zoster after five years was seronegative at day zero. Both patients presented mild forms of herpes zoster, and no generalised disease was seen. All the patients with clinical varicella infection or herpes zoster were treated with acyclovir for 10 days.

DISCUSSION

This study shows that the majority of the renal transplant children had antibodies against VZV before transplantation. Significantly more patients were seropositive after the natural varicella infection than after vaccination, and the

antibody titres were also significantly higher in the group with a previous infection. This latter finding has, to the best of our knowledge, not previously been reported. During follow-up, a greater loss of VZV immunity was seen in the vaccination group than among those with a history of varicella infection. Our results also indicate that vaccination protected to a lesser extent from symptomatic VZV disease, but provided effective protection against life-threatening disease.

In the present study, the proportion of VZV seropositive children following pre-transplant vaccination was lower than reported in two previous studies showing seroconversion rates of 80% and 77%, respectively, one year after transplantation (18,27). This discrepancy could be due to differences in vaccination protocols, different time intervals between vaccination and VZV serology determination, diverse serological methods and cut-offs being used, as well as variations in patient age and morbidity (10,11,17,18).

A limitation of our retrospective study was that we were not able to find out exactly how many vaccine doses each patient had received prior to transplant. All patients transplanted from 2005 onwards received two doses, and before that date, they received one or two vaccine doses before transplantation. The serostatus did not differ when the two cohorts were compared. However, five of the seven vaccinated cases with post-transplant symptomatic varicella infection and four of the five vaccinated cases with asymptomatic infection after transplantation occurred in children who had been vaccinated before 2005.

When measuring VZV antibodies over time after renal transplantation, we showed that varicella-vaccinated individuals lost their seropositivity to a larger extent than

previously infected individuals. The impact of age on the maintained vaccine-induced immunity to VZV could not be excluded, as the vaccinated children were younger than the previously infected children. Nilsson et al. found that intensive chemotherapy for childhood acute lymphoblastic leukaemia induced loss of humoral immunity to viral vaccine antigens in a high proportion of children, especially younger infants (28). It has been previously reported that when the varicella vaccine was given to children with renal insufficiency pre-transplant, combined with immunosuppressive treatment after transplantation, it induced less persistent antibody levels in comparison with historically reported values in healthy vaccinated children (17,29). In a study published in 2017, the VZV infection was demonstrated to produce lifelong immunity in healthy individuals, whereas seropositivity after VZV vaccination was estimated to decrease by 8% for each year that had elapsed since vaccination (30). Broyer et al. studied paediatric renal transplant candidates who were seropositive after the natural varicella infection and found that they lost VZV antibodies after grafting: 0.4% after one year, 2.8% after two years and 4.5% after five years (17). These numbers are in agreement with what was found in the present study, where only one of 38 children lost seropositivity about four years post-transplant. Broyer et al. also reported that among varicella-vaccinated children who underwent renal transplantation in 1980–1992 and were seropositive at transplantation, 7% had lost VZV IgG after one year, 11% after two years and 24% after five years (17). In another study, Furth et al. reported that 23 vaccinated children, including 16 who received renal transplants, remained seropositive three years post-vaccination and 87% had antibody levels that were considered to be seroprotective (19). In our study, the vaccinated patients lost VZV IgG with a higher frequency, as 14% became seronegative one year after their transplant and 61% two years post-transplant. The results of our study cannot be directly compared with the other studies, as the patients were not treated with the same immunosuppressive drugs and the serological analyses and cut-off levels differed. The relatively low VZV antibody levels at transplantation might also explain the early loss of seropositivity in our vaccinated patients.

In 1994, Zamora et al. reported that one dose of the Oka-attenuated varicella vaccine was safe and efficacious, not just in 17 pre-transplant children on chronic dialysis, including 13 who received renal transplants during the follow-up period, but also in 17 children after renal transplantation (21). Although our study cannot be directly compared with their investigation, the breakthrough infections are similar to ours. In their study, three of the 30 vaccinated renal transplant recipients, who had initially been seropositive after vaccination, presented an attenuated form of varicella two to four years post-vaccination. In our study, seven of the 38 children who had been vaccinated before transplantation developed a mild form of varicella. In addition, five cases of asymptomatic reactivation of VZV were found among the vaccinated children. The probability of not suffering VZV disease was significantly higher in the

group with previous varicella infection in comparison with those who had been vaccinated. However, the difference in hazard ratios between the groups was not statistically significant when adjusted for age. It is noteworthy that breakthrough symptomatic varicella infection was only observed in patients who had no detectable antibodies at the time of grafting or had lost their antibodies after transplantation. These results are comparable with earlier data published by Broyer et al. (17). Seronegativity, which evolves over time, does not necessarily indicate a loss of immunity. This could be due to the presence of cellular immunity, which was not analysed in our study but should be studied in future investigations. Another limitation of our retrospective study was the relatively low number of participating children along with the fact that approximately 13 of the children were lost during the serological follow-up, due to lack of serology sampling post-transplant. The strength of our study is that we were able to compare VZV immunity and infection outcomes in renal transplant children who had experienced natural varicella infection with those who had been vaccinated. The number of children who are currently experiencing natural varicella is diminishing as most countries have introduced the VZV vaccine to their routine vaccination programmes for children.

CONCLUSION

Our data indicate that a serologically proven history of varicella provided protection from symptomatic varicella infection in renal transplant patients. Varicella vaccination protected to a lesser extent from symptomatic VZV infection, but provided effective protection from life-threatening disease, even though the antibodies were below the cut-off level. In our study, previously varicella-infected patients predominately acquired reactivated herpes zoster, while the vaccinated patients developed varicella. Based on our observations, and those of other studies, we suggest that varicella antibodies should be monitored regularly after vaccination in individuals who are immunosuppressed due to underlying disease and/or treatment. If a loss of a previously protective VZV antibody titre occurs, or if vaccination does not induce seroconversion, an additional vaccine dose could be considered. In addition, we suggest that VZV serology is measured in children when renal failure is detected, so that varicella vaccination can be administered. Serological determination should also be obtained at least three months before a planned renal transplant so that an additional vaccine dose can be given. Further studies involving larger patient cohorts are warranted, to determine the periodicity of VZV antibody monitoring and booster vaccination.

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CONFLICTS OF INTEREST

The authors have no conflict of interests to declare.

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