PEPtalk2

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PEPtalk2: Results of a pilot randomised controlled trial to compare VZIG and aciclovir as post-exposure prophylaxis (PEP) against chickenpox in children with cancer

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Abstract

Objective: To determine the likely rate of patient randomisation and to facilitate sample size calculation for a full-scale Phase III trial of VZIG and acyclovir as post-exposure prophylaxis against chickenpox in children with cancer

Design: Multi-centre pilot randomised controlled trial of varicella zoster immunoglobulin (VZIG) and oral aciclovir

Setting: England, UK

Patients: Children under 16 years of age with a diagnosis of cancer: currently or within 6 months of receiving cancer treatment and with negative varicella zoster virus (VZV) serostatus at diagnosis or within the last 3 months.

Interventions: Study participants who have a significant VZV exposure were randomised to receive PEP in the form of VZIG or aciclovir after the exposure

Main outcome measures: Number of patients registered and randomised within 12 months of the trial opening to recruitment and incidence of break-through varicella

Results: The study opened in 6 sites over a 13 month period. 482 patients were screened for eligibility, 32 patients were registered and 3 patients were randomised following VZV exposure. All 3 were randomised to receive aciclovir and there were no cases of break-through varicella.

Conclusions: Given the limited recruitment to the PEPtalk2 pilot, it is unlikely that the necessary sample size would be achievable using this strategy in a full-scale trial. The study identified factors

that could be used to modify the design of a definitive trial but other options for defining the best means to protect such children against VZV should be explored.

Background

Of the approximate 1500 children newly diagnosed with cancer annually in the UK and the Republic of Ireland, almost 25% lack immunity to varicella zoster virus (VZV), the cause of chickenpox and shingles (1). Treatment-related immunosuppression and for certain cancer types, the disease itself place these individuals at high risk of severe infection. In healthy children, primary VZV infection usually follows a benign clinical course and significant complications are uncommon (2). By contrast, infection in immunocompromised patients can result in treatment delays, significant morbidity and even mortality (3-7).

Current guidelines for this group of patients emphasise the importance of minimizing their contact with VZV, and of providing post-exposure prophylaxis (PEP) should this occur. A report on use of PEP in children with cancer in the UK and Republic of Ireland suggested that PEP is delivered to approximately 250 children with cancer annually (1). However, there is a striking lack of consensus on which PEP is best for this group. The gold standard has been an injection of varicella zoster immune globulin (VZIG) to be given as soon as possible after exposure. VZIG is prepared from pooled plasma of donors with suitably high titres of VZV IgG antibody. The use of VZIG is supported by evidence from historical studies (3, 8-10). However, there is a widely reported range of efficacy of VZIG, depending on exposure and level of immunosuppression (10, 11). VZIG is associated with injection discomfort, inconvenience and significant cost. Furthermore, due to a theoretical risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) from plasma products, VZIG used in the UK is now prepared from plasma sourced from outside the UK, and its supply is limited by the availability of suitable donors (12). Lack of suitable donors may intensify as varicella-immunised individuals begin to enter adulthood in the USA and other countries which currently are the source of the VZIG used in the UK.

Aciclovir, an oral antiviral drug that is effective in the treatment of VZV and herpes simplex virus (HSV) disease, has been used as an alternative means of PEP in some UK paediatric oncology centres for over twenty years (1, 13). A national guideline of the Royal College of Paediatrics and Child Health (RCPCH) published in 2002, proposed VZIG and aciclovir as equivalent alternatives as PEP in this patient group (14). However, Public Health England's Green Book publication on varicella, updated in 2015, recommends only VZIG as PEP for immunocompromised children and does not include aciclovir as an alternative (12). Small observational studies in healthy children have reported varicella rates of 0-77% after using aciclovir as PEP (15-17). In immunocompromised children, a few small retrospective studies describe no breakthrough varicella infections following aciclovir as PEP while others report a rate of 3-22% (18-23).

To date, no randomised trials have compared the efficacy of VZIG and aciclovir as PEP in immunocompromised patients. The PEPtalk feasibility study reported that varicella exposures are frequent but that the approach to PEP in paediatric cancer patients is highly polarised among centres (1). Patients are given VZIG or aciclovir in approximately equal measure. Opinion is strongly polarised among UK paediatric oncologists who prescribe PEP on the basis of unit policy and experience and not necessarily patient preference. Furthermore, there are systematic differences in practice surrounding the delivery of PEP among centres using VZIG compared with aciclovir (such as definitions of exposure and policies concerning the re-checking of serology prior to administration of PEP). These considerations suggest that only a well-powered randomised controlled trial could provide evidence of a quality sufficient to support a change in practice. The main objective of this pilot study was therefore to determine the likely rate of patient recruitment and randomisation and to facilitate sample size calculation, in order to inform the design of a larger trial.

Methods:

This pilot study was a UK-based multi-centre randomised controlled trial between VZIG and oral aciclovir as PEP in children with cancer. Study participants were recruited over a 13-month period from May 2014 until June 2015 from 6 hospitals.

Study eligibility:

The study was open to all children under 16 years of age with a diagnosis of cancer who were either receiving or within 6 months of receiving immunosuppressive treatment for cancer. Children who had a current or previous allogeneic or autologous haemopoietic stem cell transplant were excluded from the study. To be eligible for the study, children were required to be VZV seronegative at the time of diagnosis or within the previous 3 months.

Study design:

VZV seronegative children were randomised to receive either VZIG or aciclovir following a significant exposure to varicella. The definition of significant exposure included any household exposure, non-household exposure by means of: contact in the same room, e.g. in a classroom or a two-to four-bed hospital bay, for 15 minutes or more or face-to-face contact, e.g. while having a conversation (12). Registration and randomisation were carried out by telephone by the Cancer Research Clinical Trials Unit, University of Birmingham. Patients were randomised using simple randomisation with a restriction to state that if an imbalance of greater than 2 should occur the next patient would be allocated to the smaller of the treatment arms.

Consent:

As PEPtalk2 had a two-stage enrolment process, beginning with registration and then followed (in the event of a chickenpox exposure) by randomisation, written informed consent from the patient's legal representative was obtained at both stages.

Study procedures:

Blood for VZV serology was taken at the time of exposure and at 12 weeks (+/- 2 weeks) following exposure. Patients and their families were given a PEP*talk*2 Treatment Diary (including both trial-specific questions and a standardised EuroQol EQ-5D questionnaire) to record their experiences and to collect information about the impact on quality of life. Clinicians involved in caring for children participating in the trial were sent a survey to obtain their views on the randomisation process and the trial in general.

Outcome measures:

The primary outcome measure was the number of patients randomised within 12 months of the trial opening to recruitment. Considered in relation to the number of patients registered and the number of patients screened, this would allow an informed evaluation of the trial enrolment rate amongst eligible patients.

Secondary outcome measures included seroconversion rates, incidence of break-through varicella, quality of life assessments, clinicians' views and cost effectiveness. All analysis conducted was descriptive. For continuous data means with standard deviations or medians with interquartile ranges are presented, while for binary data the number and percentage are reported.

Results:

A total of 482 patients were screened for eligibility from 6 centres over the study period. Of these, 32 patients were registered and 3 patients were randomised following VZV exposure. All 3 were randomised to receive aciclovir. All 3 were seronegative at 12 weeks post exposure and there were no break-through varicella infections.

Figure 1: Consort diagram

A consistent proportion of patients were not eligible for registration because they were seropositive (ranging from 65-70% by month, overall 70%). Those with indeterminate results were also not eligible for registration and this proportion declined over the first 6 months of the course of the trial, from 20% to 13%, and then remained steady at 11-13% for the remainder of the trial (overall 12.3%).

The proportion of patients that were seronegative and therefore eligible for participation (n=76, 16%) was also consistent over the study period (12% for the first month and then 14-17% by month). Seronegativity status varied by age: 50% in 2-4 year olds, 21.1% in 5-7 year olds, 5.3% in 8-10 year olds and 7.9% in >10 years of age. The median age of seronegative patients was 3.8 years.

Figure 1 also shows the reasons for declining to be registered (n=44, 57.9%). The major reason given was the distance of travel to the trial site (n=23, 52%). The other main reasons were the need for additional oral medication (n=6, 14%) and the need for additional blood samples (n=8, 18%). Personal communications with local staff indicated that families who declined due to the need for further oral medication did so as the patient(s) did not have nasogastric tubes anymore and had struggled with oral medications previously, or that the patient was back at school and taking oral medications during school time was an issue for them.

Outcome measures

Three patients were randomised to receive PEP (9% of registered patients). The age of the 3 patients was 5.8, 6.1 and 6.8 years. For two patients, the source of contact was a sibling and in the other it was a source outside the household. The 3 were all randomised to receive aciclovir and all 3 were assessed as being compliant with the full course. No patient withdrawals were reported and no patients were found to be ineligible post randomisation. There were no cases of varicella among the patients and none seroconverted between exposure and the 12 week follow-up. Cost effectiveness analysis could not be conducted as there were no events in the VZIG arm. As no hospital admissions

were reported no cost effectiveness could be calculated. No adverse events, serious adverse events or deaths were reported in the trial. Quality of life questionnaires were returned for all 3 randomised patients (complete data for 2).

Clinician surveys

Feedback was recorded from all participating clinicians (n=8). Specific feedback included that the patient information sheet could be condensed further, that the effort taken in registering patients should be recognised in terms of portfolio accruals, that shared care centre involvement was important, and that routine practice currently does not require serological screening of patients with a history of VZV contact.

Discussion:

The main objective of this pilot study was to determine the likely rate of patient randomisation and to facilitate sample size calculation, in order to inform the design of a larger trial addressing the issues around post exposure prophylaxis in this population (24). It was estimated that if, for example, the pilot study was successful in recruiting 50 patients from up to seven UK centres over a 12-month period, then a larger trial that recruited from twice as many centres over a 24-month

period was realistic and could recruit around 200 patients. This was seen as achievable in a UK network. If found to be necessary the trial size could also be increased further, but an international consortium would then likely be required to achieve this. This main objective was therefore achieved.

The finding that the pilot study randomised only 3 patients from 6 centres over a 13-month study period indicates that recruitment of sufficient numbers to a definitive and similarly designed trial would not be achievable. As intended, the pilot study has allowed us to identify a number of reasons for this low rate of recruitment and indeed, with this knowledge, a number of these could now be avoided in the design of a further trial - but nevertheless, a different approach to addressing the issues around PEP will likely be needed. This study revealed a lower probability of being seronegative among trial participants than expected. Undertaking this pilot study was more efficient than attempting a large definitive trial which would have failed to achieve its recruitment targets and wasted money, time, and the voluntary efforts of the families involved. It is difficult to interpret the value of QOL scores from only 3 patients (complete data for 2) but this will be important to consider in future trial planning.

Only 6, rather than 7, sites were able to participate in the pilot study and of these only 2 were able to participate for the full trial period. Choice of sites might be critical as one site dominated in terms of registration (15/32).

An important eligibility criterion was omitted from the original protocol i.e. being up to 6 months post cancer treatment. This was introduced as a later amendment and may have had some impact (likely small) on the recruitment rate. Furthermore, it would be important to include haematopoietic stem cell transplant recipients in future studies as prophylactic regimens to prevent VZV infection in

this group are also controversial and vary widely (25). This group was excluded from the pilot study design due to low projected patient numbers in the study centres, heterogeneity of conditioning regimes and underlying diagnoses and variation in the use of prophylactic aciclovir in these patients.

The rate of seronegativity (16%) found in this study was lower than predicted (24%) (1). An important factor here was the high rate of indeterminate results (around 13%). Not to have incorporated this eventuality in the protocol was an important omission as in practice such cases should be considered as potentially susceptible and therefore recommended to receive post-exposure prophylaxis. Additionally, it was not routine practice to reassess status in those with a history of VZV or who are found to be VZV seropositive at diagnosis. This should also have been addressed in the protocol and repeat serology obtained on such children. This may have increased the number of potentially eligible children for registration. We and others have shown that children can lose their immunity over the course of treatment and become seronegative (26-28).

The reasons given for not agreeing to participate are important and this knowledge would allow adjustments to be made to future trials. For example, it would be important to ensure that all hospitals (shared care sites) that fall into the recruitment areas of major sites are engaged in the study so that travel for patients is minimised.

Concern was evident regarding the need for blood samples and these could be reduced in a future trial, for example the need to repeat serology again at randomisation. Furthermore, testing of oral fluids may be a more acceptable way of ascertaining serology, rather than blood samples in the future (29).

During the trial period there was a lower rate of VZV exposure (10%) than originally predicted (20%). Although accurate data on the rates of VZV exposure and disease are not available for UK children with malignancy, a 20-30% risk of varicella exposure during a child's mean 2.5 years of maintenance therapy for ALL has been calculated. (30) In another study of 86 children followed through the duration of ALL treatment there were 26 episodes of varicella and herpes zoster, of which 17 occurred during maintenance therapy. (31) There is also some indication that exposure of the general population during this time period was also lower than in other years. Clearly, had we identified susceptible children earlier in the trial period and then followed them for a longer period of time (as could be done in a definitive trial), there would have been greater exposure to VZV and this would have minimized the impact of seasonal variations in VZV exposure.

This pilot study suggests that it will likely be too challenging to undertake a definitive, non-inferiority trial of these 2 forms of PEP in a UK-only study. In the original considerations around the trial, and assuming a relatively large non-inferiority margin of 10%, it was estimated that about 450 patients would be needed with a one-sided alpha of 0.05 and 80% power; if the alpha were to be relaxed the number would be reduced (with alpha=0.1, n=350; alpha=0.15, n=280; alpha=0.2, n=240). A smaller trial might however, be considered to be reasonable as two standard treatments are being compared, as opposed to comparing a standard treatment with a novel agent.

Is a definitive randomised trial still required? In the UK, we do not have a routine varicella vaccine program in place, in contrast to a number of other industrialised countries. Such countries have seen a dramatic decline in the incidence of varicella in their childhood population in both their vaccinated and unvaccinated populations through herd immunity. VZV remains an issue in children with cancer

in all countries without routine immunisation programmes (32-34). The UK Joint Committee on Vaccination and Immunisation (JCVI) is currently reviewing the status of the VZV vaccine; even if introduced it's impact on this population would not be felt for some time.

The equipoise between aciclovir and VZIG as the best way of providing post exposure prophylaxis remains. No substantial data have been published in the interim that suggest one is superior to the other. One study only (published in Spanish), refers to the experience in one centre where both PEP options are available with no reported adverse effects in relation to the different prophylaxis measures nor any secondary cases observed at 30 days (19). When treating children with cancer, it is imperative to have reliable evidence rather than to depend on belief and it may be that some clinicians should reconsider their recommendation of PEP for patients.

The lack of published evidence for the effectiveness of aciclovir represents a major barrier to informed decision-making. Historically, no prospective UK surveillance data have been collected to document the occurrence of varicella in relation to the mode of PEP whereas this may now be an appropriate methodology to pursue. The implications of reaching consensus on whether aciclovir is at least equivalent to VZIG as post-exposure prophylaxis would reach well beyond UK paediatric oncology practice.

Conclusions

We conducted a pilot, randomised controlled trial of post varicella exposure prophylaxis in children with cancer, in order to determine the likely rate of randomisation and to facilitate sample size calculation for a definitive trial. Over a 13 month period we screened 482 children, registered 32 and randomised 3 children, from among 6 trial sites. A number of issues were identified that could be used to modify the design of a definitive trial but overall our experience suggests that the necessary

sample size is not achievable using this recruitment strategy. Other options for defining the best means to protect such children against VZV should be explored.

What is already known on this topic:

- Chickenpox is a frequent and potentially serious risk for paediatric oncology patients
- There is no consensus as to which type of post-exposure prophylaxis is best

What this study adds:

- A randomised controlled trial of VZIG and aciclovir is unlikely to be feasible in this patient population and a different approach will be required to address this issue

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Figure 1: Consort Diagram

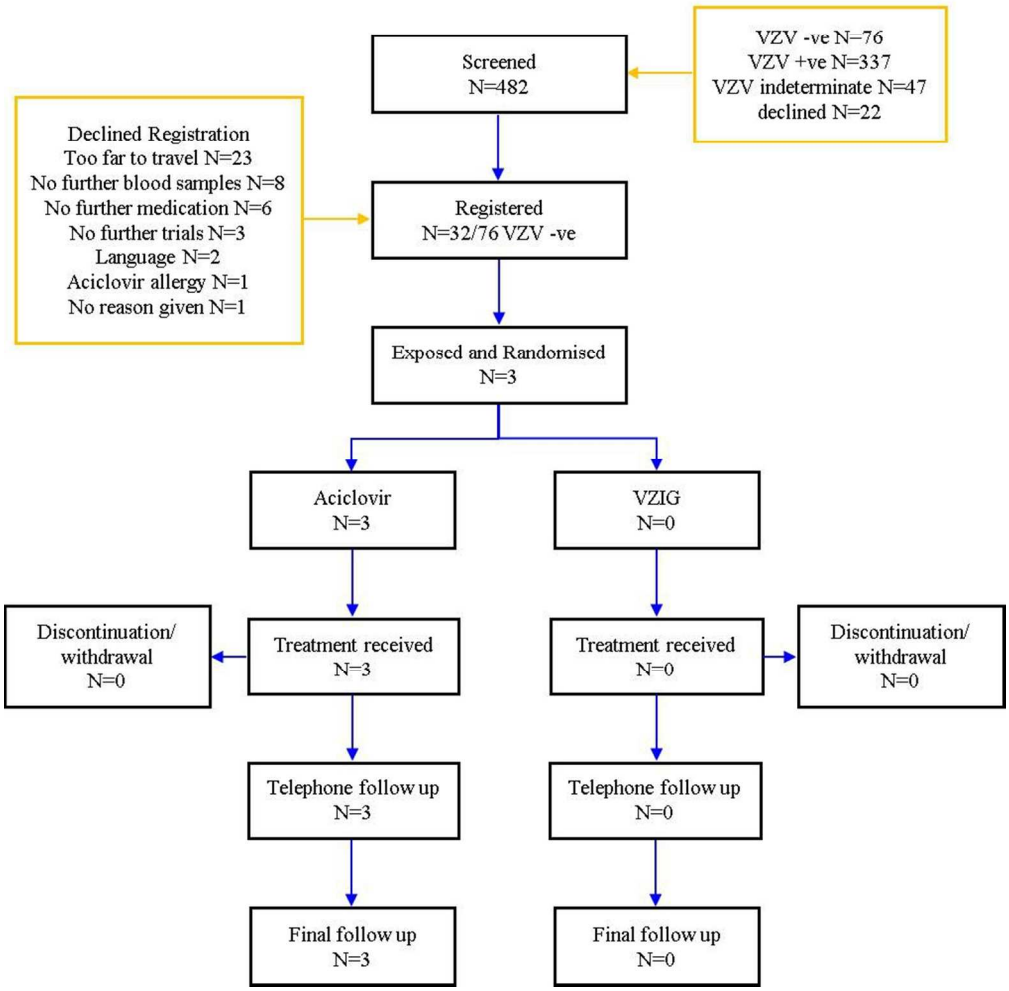

Figure 1: Consort Diagram

171x180mm (150 x 150 DPI)