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Efficacy and long-term outcomes of palivizumab prophylaxis to prevent respiratory syncytial virus infection in infants with cystic fibrosis in Northern Ireland

Running Title: Use of palivizumab to prevent RSV in CF patients

Author(s): H.E. Groves, L. Jenkins, M. Macfarlane, A. Reid, F.Lynn, M.D. Shields

Institute(s):
1 Royal Belfast Hospital for Sick Children, Paediatrics, Belfast, United Kingdom
2 Royal Belfast Hospital for Sick Children, Cystic Fibrosis Department, Belfast, United Kingdom
3 School of Nursing & Midwifery, Queen’s University Belfast, Belfast, UK
4 Queens University of Belfast, Professor of Paediatrics, Belfast, United Kingdom

Corresponding Author:
Dr Helen Groves
20 Brookvale Road, Rathfriland, Co.Down, Northern Ireland
BT345DA
Tel: 00447745343921
Email: hgroves01@qub.ac.uk

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ABSTRACT

Background: RSV causes considerable morbidity and mortality in children. In cystic fibrosis (CF) viral infections are associated with worsening respiratory symptoms and bacterial colonization. Palivizumab is effective in reducing RSV hospitalisation in high risk patient groups. Evidence regarding its effectiveness and safety in CF is inconclusive. CF screening in N. Ireland enabled timely palivizumab prophylaxis, becoming routine in 2002.

Objectives: To determine the effect of palivizumab on RSV-related hospitalization and compare lung function and bacterial colonization at age 6 years for those born pre and post introduction of palivizumab prophylaxis.

Methods: A retrospective audit was conducted for all patients diagnosed with CF during the period from 1997 to 2007 inclusive. RSV-related hospitalization, time to *Pseudomonas aeruginosa* (PA) 1st isolate, lung function and growth parameters were recorded. Comparisons were made for outcomes pre and post introduction of routine palivizumab administration in 2002. A cost evaluation was also performed.

Results: 92 children were included; 47 pre and 45 post palivizumab introduction. The overall RSV-positive hospitalization rate was 13%. The relative risk of RSV infection in palivizumab non-recipients versus recipients was 4.78 (95% CI: 1.1 – 20.7), p 0.027. Notably, PA 1st isolate was significantly earlier in the palivizumab recipient cohort versus non-recipient cohort (median 57 versus 96 months, p< 0.025) with a relative risk of 2.5. Chronic PA infection at 6 years remained low in both groups, with similar lung function and growth parameters. Total costs were calculated at £96,127 ($151,880) for the non-recipient cohort versus £137,954 ($217,967) for the recipient cohort.

Conclusion: Palivizumab was effective in reducing RSV-related hospitalization infection in CF patients. Surprisingly, we found a significantly earlier time to 1st isolate of PA in palivizumab recipients which we could not explain by altered or improved diagnostic tests.
INTRODUCTION

Respiratory syncytial virus (RSV) is the most frequent cause of lower respiratory tract infection (LRTI) in young children and by the age of two years, 80% of children have encountered the infection.¹,² Risk factors pre-disposing to severe RSV-related lower respiratory tract infection (LRTI) include prematurity, bronchopulmonary dysplasia, congenital heart disease and immunodeficiencies.³⁻⁶ In patients with cystic fibrosis (CF) viral infections have been shown to be associated with increased hospitalization rates and decline in pulmonary function, resulting in short-term and long-term morbidity.⁷⁻¹⁰ A marked inflammatory response to RSV infection in patients with CF has been observed, with reported hospitalization rates up to 14.6%.¹¹,¹² These infants often have a prolonged hospital admission and some studies have noted a greater decline in lung function among infants with CF with a history of RSV-related hospitalization than those who did not require admission.¹²

No vaccine against RSV is currently available and treatment of RSV bronchiolitis is largely symptomatic. The monoclonal antibody Palivizumab is the only preventative therapy. It has proven efficacy and safety against RSV in randomized controlled trials involving preterm infants < 35 weeks’ gestational age, children aged < 2 years with severe chronic lung disease and haemodynamically significant congenital cardiac disease.¹³,¹⁴ Use of Palivizumab in the CF population is not widespread practice. Recent surveys revealed its use in only 8.8% of UK centres, with higher usage within North American centres, 75% in the US and 60% in Canada.¹⁵,¹⁶ The recent Cochrane review by Robinson et al. identified only one randomised control trial on the use of palivizumab for prophylaxis against RSV infection in CF. This study found admission rates were not decreased, however RSV incidence was very small and the review determined that evidence is insufficient to draw conclusions on the efficacy and safety of palivizumab in this group.¹³,¹⁷

Few studies have investigated the use of palivizumab therapy to prevent RSV in CF. Most are non-randomised, involving small numbers of patients with limited follow-up periods and inconclusive results.¹¹,¹² One US study in a large CF population found potential benefits to using palivizumab however results were inconclusive due to the small event rate of RSV-related hospitalization.¹⁸ A recent meta-analysis has found that prophylactic treatment with palivizumab may be effective in reducing hospital admission rates due to RSV-related LRTIs.¹⁹
In Northern Ireland screening for cystic fibrosis has taken place since the 1980s. Early identification of affected infants enabled the introduction of routine palivizumab administration for since 2002. This was given to all CF infants at the start of their first RSV season regardless of age with further doses in their second season for high-risk infants or those less than 1-year-old. This population therefore provides a unique opportunity to examine the effect of palivizumab use in CF patients on rates of hospitalisation secondary to RSV-related LRTI, as well as long term follow-up of its impact on lung function and bacterial colonization rates.

METHODS

Design
We undertook a retrospective audit of outcomes for children born during the period from 1997 to 2007 at the Northern Ireland Regional Paediatric Cystic Fibrosis Centre. Our primary objective was to compare RSV-related hospitalization in the cohort of children born pre palivizumab prophylaxis (1997 to 2002 inclusive) with the cohort of children in the period post palivizumab prophylaxis (2002 to 2007 inclusive). Our secondary objectives were to assess lung function, growth parameters and bacterial colonization in the two cohorts when each child had reached the age of 6 years.

Only children diagnosed via the neonatal screening program were included. Those born outside of Northern Ireland and therefore not diagnosed on screening were excluded as they could not have been offered timely palivizumab.

Data Collection
All patients were identified from the patient registry at the Northern Ireland Regional Paediatric Cystic Fibrosis Centre. Baseline data were available to establish patient demographics, neonatal course and genotype. Whether or not palivizumab was received, age of first dose and number of doses received were recorded for each patient. Primary outcome data were recorded for hospital admission secondary to RSV-related LRTI, including duration of stay.

Secondary outcomes were noted for all patients, including age at first isolate of *P. aeruginosa* (PA), as well as presence of chronic colonisation. Growth parameters, including height (cm), weight (Kg) and BMI at age 6 years and forced expiratory volume in one second (FEV1, % predicted) at age 6 years were recorded for both cohorts.

Parental consent is obtained as standard for patient data to be included in a national online database that may be used anonymously for audit and research purposes. This audit was
conducted as part of a hospital service evaluation and therefore ethical approval was not required.

Definitions

Genotype was defined according to the presence of delta F508 deletion and recorded for each patient as homozygous F508del mutation, heterozygous F508del mutation or other (no F508del mutation).

RSV-positive hospitalization was defined as any hospitalization for respiratory symptoms during which it was determined that the infant had an RSV-positive infection by polymerase chain reaction testing of nasopharyngeal secretions. In our unit all CF patients admitted to hospital with respiratory symptoms routinely undergo viral testing of nasal secretions. Importantly, all CF patients are managed in the Paediatric CF unit in Belfast and do not attend peripheral hospital units for care, ensuring all hospital attendances are recorded centrally.

Presence of bacterial colonisation was identified from individual bacteriology result records. All bacteriology samples from the unit are processed using standardised techniques in the microbiology laboratory at the Royal Victoria Hospital, Belfast. Cough swabs are taken at least three monthly from birth as part of the routine care of every CF patient at the centre and more frequently in periods of illness during which cough swabs and/or sputum swabs will additionally be taken. *P. aeruginosa* chronicity was defined as having $\geq 3$ discrete *P. aeruginosa* positive nasal/cough swabs or sputum culture results within a one year period.

Health economic evaluation

A basic health economic evaluation was conducted to compare costs of palivizumab prophylaxis versus costs saved. Administration of palivizumab occurred during routine clinics at the Northern Ireland Regional Paediatric Cystic Fibrosis Centre, performed by a specialist nurse (client contact time 15 minutes). Resource use, including palivizumab administration, hospital stay and follow up were costed in UK Sterling (£) (dollars calculated using 2013/2014 average exchange rate) using unit costs from the National Schedule of Reference Costs 2013-2014\textsuperscript{20}, the British National Formulary\textsuperscript{21}, and the Personal Social Services Research Unit\textsuperscript{22} (see supplementary table). These data were used to calculate total costs for each cohort. No discounting of costs was applied, as the time horizon was less than 1 year.

Statistical analyses
Descriptive data is summarised as means (standard deviations, SD) or medians (interquartile ranges). Children receiving palivizumab (those born after routine introduction in 2002) were compared to those who did not receive palivizumab (those born before routine introduction). Comparisons were made between cohorts using data collected aged 6 years. The primary endpoint for comparison was hospitalization for RSV-related respiratory infection (Yes v No), analysed using Fisher’s exact test. Secondary endpoints were Weight, Height, BMI and FEV1 (% predicted) values at 6 years old. Student t-tests, Chi Squared and Fisher’s exact tests were used.

Time to acquisition of PA was compared between those receiving palivizumab and those not using the Wilcoxon test. We used Cox’s proportional hazard regression to determine whether those receiving palivizumab (Yes v No) had the same effect on time to acquisition of PA independently of genotype (homozygous, heterozygous, other) and gender. A p-value of < 0.05 was taken as statistically significant. JMP version 12.1 (® SAS) software was used for analyses and survival curve analysis graphs were produced using GraphPad Prism version 5.03 for Windows (GraphPad Software, La Jolla California USA).

RESULTS

Subjects

A total of 98 cystic fibrosis patients were identified as being born during the defined period, 6 were excluded due to being born outside Northern Ireland. All patients in the palivizumab recipient cohort (those born after 2002, n=45) received palivizumab in their first year of life before the onset of the RSV season. The average age at first dose of palivizumab was 99.4 days old and the average number of doses received was 5.1 (SD= 2.0).

A greater proportion of males (p=0.031) were noted in the palivizumab non-recipient cohort (table 1). Statistically similar numbers of CF affected first degree relatives (p=0.14) were observed in both cohorts, with similar CF genetic mutation classes observed (p= 0.45).

RSV-Positive Hospitalizations

The overall RSV-positive hospitalization rate is 13%. Relative risk of RSV infection in palivizumab non-recipients versus recipients is 4.78 (95% CI: 1.1 – 20.7). Those who received palivizumab were significantly less likely to be admitted to hospital for RSV-related LRTI than non-palivizumab recipients: 2 / 45 versus 10/47, p=0.027 (median duration of hospital stay 3 versus 10 days).
For one patient in the palivizumab non-recipient cohort data was not available for duration of hospital stay secondary to RSV-related LRTI.

**Growth parameters**

No significant difference was noted for weight, height or BMI at age 6 years between palivizumab and non-palivizumab recipients (table 2).

**Lung function testing**

No significant difference was evident between FEV1 (% of predicted value) at 6 years of age between cohorts (Table 2). No difference was noted in FEV1 at 6 years of age in patients with RSV-related hospital admission versus non-admission regardless of palivizumab status.

**Bacterial colonisation rates**

Of note, there was a significant difference in the median time to first isolate of PA between cohorts with a significantly earlier time to first isolate noted in the palivizumab recipient cohort. Using survival analysis modelling (Figure 1), the median time to *P. aeruginosa* first isolate in the palivizumab non-recipient cohort was 96 months versus 57 months in the palivizumab recipient cohort (Wilcoxon test, p 0.025).

The risk ratio of PA first isolate in males versus females (irrespective of palivizumab status) was 2.05, p 0.006. PA first acquisition by genotype is illustrated in figure 2. The relative risk of PA first isolate for homozygous F508del versus other genetic mutations was 4.5 (p <0.001) and overall, males with homozygous F508del mutation had the highest risk of first PA acquisition irrespective of palivizumab status.

Having adjusted for gender and genotype, the relative risk of PA first isolate during the study time period in the palivizumab recipient cohort versus non-recipient cohort was 2.5, p 0.001 (95% CI: 1.44 – 4.2).

The separation in survival curves is noted to occur from 2 months of age. Two infants noted to have PA acquisition at 2 months of age both received palivizumab at 24 days of age.

Importantly, no significant difference was noted for chronic *P. aeruginosa* infection rates at 6 years old between cohorts. Only 3 patients had chronic *P. aeruginosa* infection aged 6 years in the palivizumab non-recipient cohort and 2 patients in the palivizumab recipient cohort.

**Health economic evaluation**
From a UK National Health Service perspective, the total costings for the palivizumab recipients over the time period were £137,954 ($217,967) and in the palivizumab non-recipient group costs amounted to £96,127 ($151,880), as shown in table 3. The estimated costs of palivizumab and its administration over the five years post introduction are £133,794 ($211,394) and the estimated costs saved from reduced RSV-related hospital stay in palivizumab recipients (compared to non-recipients) are £91,967 ($145,307).

DISCUSSION

To our knowledge, this is the first long-term follow up of CF infants following palivizumab prophylaxis for RSV. We found a significant reduction in RSV-related hospitalisation in patients who received prophylactic palivizumab versus those who did not. However, in view of the small numbers included in this study it is difficult to make robust statements on this outcome. A recent study in Limerick, Ireland, did not demonstrate any significant difference in outcomes with palivizumab use, although notably, this study was not conducted in a screened population.23 Our study represents a unique opportunity to present outcomes in a screened population where care is provided by a single team delivering standardised care over the duration of the period studied.

Reduced lung function following RSV infection in CF patients has been noted in previous studies at follow-up times less than one year.12 Our findings did not demonstrate any significant difference in lung function at 6 years between cohorts despite reduced RSV infection rates with use of palivizumab. A possible explanation for this is that any deterioration in lung function may be a short term effect, not persisting into early childhood. Of note, FEV1 may not be the most sensitive measure of lung damage in CF patients and is often preserved in this age group. Alternative measures of lung function may prove more useful in this context. The lung clearance index (LCI), for example, reflects abnormalities of the small airways and therefore detects earlier signs of lung injury in CF which may be different between groups at this early age.24 However, at present, alternative lung function measurements such as LCI are not undertaken at our centre and were therefore unavailable for comparison.

Limited data exists on other important outcomes in relation to palivizumab prophylaxis in CF patients, particularly in relation to bacterial colonisation. The interaction of bacterial colonisation and viral infection in CF is not fully understood. It has been extensively demonstrated that lung function deteriorates significantly after colonisation by PA.22 Enhanced bacterial adherence to virus infected cells may facilitate bacterial colonisation in CF patients.225 60-68% of new bacterial colonisation cases are detected during the viral season and 85% of new PA colonisations occur within three weeks of a viral infection.226,27
Furthermore, human airway epithelial cells infected with RSV demonstrate enhanced binding of several species of bacteria and one study has detected a rise in antipseudomonal antibodies following viral infection in patients suffering from CF, with the strongest association after RSV infection.\textsuperscript{28}

Our findings did unexpectedly demonstrate a significant decrease in the age of first isolation of PA in patients who had received palivizumab in comparison to those who did not. These surprising results are apparently contradictory to the assumption that prevention of RSV-related LRTIs with palivizumab will lead to decreased rates of PA colonisation. Although we cannot fully exclude this we do not believe that these results can be explained by altered or improved diagnostic tests as there has been no change in how these are performed throughout the observed study period in our clinic.

It is important to emphasise that our results found low overall chronic PA colonization rates at age six years and did not show any significant difference between cohorts. This is not surprising given that aggressive eradication regimes are routinely implemented following first isolate of PA. Our findings also demonstrated a greater risk for first acquisition of PA in patients who are F508del homozygous compared to other genetics. This result is in line with recent findings from the US national prospective EPIC Observational Study on risk factors for first isolate of PA in CF patients.\textsuperscript{29}

This study has a number of limitations which merit consideration. It is an observational study taken retrospectively and only involves a single centre. Possible confounding from factors known to be associated with early pseudomonas acquisition, including, presence of affected family members, meconium ileus and genetics, were assessed between groups and no statistical difference was noted. All patients included had received flucloxacillin from birth. Throughout the included period there was no difference in lab analysis methods for detecting pseudomonas and standard care was delivered by the same members of the CF team for all patients. However, this study does not account for possible unidentified confounding factors. For example, it is impossible to account for the influence of parental smoking on results. Additionally, patients receiving palivizumab were born later and differences in care delivered within the CF unit over time may have impacted results. Better community care available in more recent years within the unit may have reduced the need for hospital admission secondary to RSV-related LRTI and thus given the appearance of reduced hospitalization in those receiving palivizumab. In relation to age of first PA isolate, changes in unit practice may have inadvertently contributed to this. However, overall rates of chronic PA in our unit have decreased since 2002. More stringent isolation measures were introduced within the unit from 2002 for both inpatients and outpatient care in association with improved hygiene.
education for parents. These measures might have reasonably been expected to result in a later age of first isolation in palivizumab recipients rather than the earlier age observed.

The cost comparison highlights the higher costs associated with a program delivering palivizumab as a prophylaxis to CF patients, from a payer perspective. This aligns with previous findings in high-risk paediatric populations, where the high costs of administering the drug were greater than the reduction in costs of hospitalisations for RSV-related LRTIs. However, caution is needed in the interpretation of this partial economic evaluation. Assumptions relating to the administration of palivizumab by a specialist nurse during routine clinics and the use of 100mg vials per dose may have underestimated the costs of prophylaxis in the recipient cohort. Likewise, the costs of hospitalisations may have been underestimated with the use of a payer perspective, with no consideration of costs in relation to antibiotic use and a lack of long-term complications of LRTIs being taken into account. The economic burden of RSV-related hospitalisations and LRTIs on patients, families and health services should be incorporated into future, full economic evaluations. With a societal perspective and the measurement of cost per quality-adjusted life years, the true cost-utility of palivizumab in CF patients may be identified.

The main strength of this study is that it includes a screened population managed within the same unit over an extended period of time where routine palivizumab prophylaxis has been introduced since 2002. An additional asset of the study is the long length of follow-up data available for analysis.

While it is likely that an unknown confounding factor may account for the apparent earlier PA acquisition in palivizumab recipients the difference merits further consideration. Given that many countries have commenced routine CF screening, timely palivizumab prophylaxis is now an option. This is a very costly therapy that will necessitate additional resources and therefore we strongly believe that a double blind randomised control trial is required with longer term follow up before this therapy becomes introduced to standard care.

CONCLUSION

This present study demonstrates reduced RSV-related LRTI hospitalisation in infants with CF who receive palivizumab prophylaxis. Of note, the partial cost analysis highlights the higher costs associated with palivizumab as a prophylaxis to CF patients compared to savings from reduced hospitalisations. Importantly, we observed an unexpected and potentially worrying trend towards earlier \textit{P. aeruginosa} first acquisition in patients with CF.
who receive palivizumab prophylaxis. We do highlight this is a sub-optimal study design and therefore no compelling conclusions can be drawn, however we add to the call for an urgent new clinical trial to clarify the efficacy and safety of palivizumab in infants with cystic fibrosis.

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