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POINT OF VIEW

Is palivizumab effective as a prophylaxis of respiratory syncytial virus infections in cystic fibrosis patients? A meta-analysis

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Abstract
Background: Infections by respiratory syncytial virus (RSV) are more severe in patients with cystic fibrosis (CF), and many CF units use palivizumab as prophylaxis; however, information about palivizumab efficacy in CF patients is almost lacking.
Methods: A literature search up to December 2012 on the morbidity of RSV bronchiolitis in CF patients and on the safety and efficacy of palivizumab in those patients was performed. A random-effects meta-analysis was conducted for those studies meeting pre-specified search criteria. Historical controls were allowed.
Results: The number of patients who received palivizumab was 354 and the hospital admission rate was 0.018 (95% CI 0.0077–0.048). The corresponding number in the non-treated groups was 463 patients with an admission rate of 0.126 (95% CI 0.086–0.182) ($Q = 13.9$; $p < 0.001$).
Conclusion: Palivizumab may have a role in the prevention of severe lower airway infection by RSV in CF patients.

Introduction

Infections by respiratory syncytial virus (RSV) have been shown to be more severe in patients with cystic fibrosis (CF) as compared to those with no prior respiratory disease, as measured either by the need for admission to the ward or to the intensive care unit (ICU); or assessed by mean duration of hospitalisation; or by changes in lung function.[1,2] Patients with bronchopulmonary dysplasia (BPD) have a similar pattern of RSV infection to that observed in those with CF, in terms of duration of hospitalisation, ICU admission, duration of ICU stay, need of mechanical ventilation or its duration.[3]

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On the other hand, an early study from 1981[4] showed that RSV infections were more common in patients who developed chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) infection during the study period, and RSV infections were frequently associated with a rise of *P. aeruginosa* antibodies in patients who harboured these bacteria, thus suggesting that previous infections with RSV is a risk factor for *P. aeruginosa* infection, or that there is a synergism between both infections. Those early results have been strengthened by more recent findings from a study which showed that 83% of new colonisations by *P. aeruginosa* occurred in a three-week period after a viral infection.[5] Furthermore, 35% of patients who had been admitted to hospital due to a viral infection suffered from colonisation by *P. aeruginosa* during the following 12–60 months. Conversely, in the same period of time, only 6% of those with viral infections not admitted to hospital were positive to *P. aeruginosa*.[6] Van Ewijk et al.[7] performed an experimental study in bronchial epithelial cells and found that previous infection of cells with RSV or the simultaneous infections with RSV and *P. aeruginosa* significantly increased the adhesion of the bacteria to cells. Moreover, the study by de Vrankrijker et al.[8] showed that mice lung homogenates co-infected with RSV and *P. aeruginosa* had a 2000-fold increase in the numbers of colony forming units of that bacterium as compared with mice infected by *P. aeruginosa* but not exposed to RSV.

The IMpact study,[9] published in 1998, demonstrated that the administration of palivizumab (monoclonal antibodies against RSV) in newborns born preterm (PT) (i.e., born at $\leq$35 weeks gestational age) and in children $\leq$24 months of age with BPD significantly reduced the rate of hospital admissions due to RSV infections. A subsequent clinical trial further showed that the drug also prevents severe bronchiolitis in children $\leq$24 months of age with haemodynamically significant heart disease.[10] Unfortunately, there is only one double-blind, placebo-controlled clinical trial, which has yet to be published as a full paper, on the safety and efficacy of palivizumab in infants with CF.[11] This study found that admission rates were not decreased by the drug during a follow-up period of six months after an RSV infection. A Cochrane systematic review in 2010 and two more recent updates,[12–14] which could only include the aforementioned trial, concluded that the drug was not useful in CF patients infected by RSV, although more trials are necessary. However, despite the lack of evidence supporting the use of palivizumab in CF patients, many CF units around the world routinely use palivizumab as prophylaxis of severe RSV bronchiolitis.[15–17]

The aim of the present meta-analysis is to shed light on the usefulness of palivizumab as a prophylaxis for severe RSV infection of the lower airways of children diagnosed of CF.

Materials and methods

Searches were focused on studies with a clinical trial scheme in which distribution to intervention or control groups were randomised, and also uncontrolled studies (case series) which measured efficacy and/or safety, were searched for. Studies were required to have been performed in individuals younger than 18 years of age and diagnosed with CF either by screening in the neonatal period or clinically thereafter. The intervention group was required to have used palivizumab as prophylaxis, and the control group might have included placebo, or other measures of infection control including isolation, hygiene measures, etc. Historic controls were allowed.

Search strategy

A bibliographic search of scientific literature was performed either electronically or manually up to December 2012. We included usual databases, such as Medline/Pubmed, Embase; Cochrane library clinical trials registry (CENTRAL); websites related to CF looked for by means of Internet search engines; websites registering ongoing clinical trials such as *Current Controlled trials* and *Clinical trials.gov*; and ISI web of Knowledge for proceedings and abstracts from congresses. No restriction was made for publication language or publishing status. The search was completed using cross-referencing from the articles found. In those cases in which additional information was required, the authors of the specific paper were contacted via The search terms were: palivizumab; respiratory syncytial virus; RSV; neonat* OR children OR infant* OR child OR preterm* (asterisks indicating that keyword included all possible derivatives); prevention OR prophylaxis OR prophylactic OR immunoprophylaxis OR prevent; cystic fibrosis.

Statistical analysis

The efficacy of palivizumab prophylaxis was assessed as the difference of hospital admission rates between the intervention and non-treated groups. From every study included in the meta-analysis a hospital admission rate was obtained. This rate was a figure between 0 and 1. The obtained rates and their corresponding variances were analysed using a random effects meta-analysis. A weighted mean rate was obtained for the intervention, and separately for the group of studies which described the outcome in non-treated patients. The mean rates were compared using the *Q*-test for heterogeneity. I squared expressed as a percentage was used as a measure of heterogeneity. All calculations were performed by means of Comprehensive Meta-Analysis software (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2.2, Biostat, Englewood, NJ, USA, 2005). The number of patients necessary to be treated to avoid one hospital admission was calculated according to the formula: NNT = 1/[(admission rate in non-treated) − (admission rate in treated)].

Results

Results from the literature search

The literature search as described above found 61 studies performed up to December 2012. The reading of their abstracts allowed 22 of them to be discarded as they were not directly focused on the aims of the present review and were considered as noise, and thus 39 remained as potentially eligible for inclusion in the analysis. A careful review of the whole text of these papers permitted the final selection of only six studies[11,15,18–21] which matched the