Allergol Immunopathol (Madr). 2015;43(3):298–303

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

POINT OF VIEW

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

M. Sánchez-Solis[a,*], S. Gartner[b], V. Bosch-Gimenez[c], L. Garcia-Marcos[a]

[a] *Pediatric Pulmonology Unit, ''Virgen de la Arrixaca'' Children's University Hospital, University of Murcia, Murcia, Spain*
[b] *Pediatric Pulmonology and Cystic Fibrosis Units, ''Vall d'Hebron'' Children's University Hospital, Autonomous University of Barcelona, Barcelona, Spain*
[c] *Neonatology Unit, ''Virgen de la Arrixaca'' Children's University Hospital, University of Murcia, Murcia, Spain*

Received 23 August 2013; accepted 21 September 2013
Available online 11 November 2013

KEYWORDS
Respiratory syncytial virus;
Bronchiolitis;
Cystic fibrosis;
Admission rate;
Prophylaxis;
Palivizumab

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]

* Corresponding author.
E-mail address: msolis@um.es (M. Sánchez-Solis).

0301-0546/$ - see front matter © 2013 SEICAP. Published by Elsevier España, S.L.U. All rights reserved.
http://dx.doi.org/10.1016/j.aller.2013.09.003

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

Table 1 Characteristics of the selected studies.

Authors	Study type	Publication type	Group characteristics	*N*
Speer et al.[20]	Prospective observational	Original	Palivizumab vs. Historical controls[1,6]	91
Giebels et al.[18]	Retrospective observational	Original	Palivizumab vs. Non-treated	35 40
McCormick et al.[15]	Questionnaire	Letter to editor	Palivizumab vs. Non-treated	14 129
Sorrentino et al.[19]	Retrospective observational	Original	Palivizumab No control group	5
Cohen et al.[11]	Randomised placebo-controlled trial	Congress abstract	Palivizumab vs. Placebo	92 94
Paes et al.[21]	Prospective observational	Original	Palivizumab No control group	117

previously established inclusion criteria. The remaining 33 were excluded for different reasons: seven were review articles; one was a letter to the editor without quantitative data; two reported clinical cases; two included duplicate data from studies that had been previously published; 18 did not meet the inclusion criteria as patients had not been diagnosed of CF; two did not include data related to the main outcome measure, i.e. admission rates; and one used different metrics which could not be transformed to make it usable (Fig. 1). A summary of the selected six studies including CF patients treated with palivizumab is shown in Table 1.

The hospitalisation rates from CF patients non-treated with palivizumab were extracted from three of the aforementioned six studies[11,15,18] which also included a group of non-treated patients, and from three additional studies which reported series of non-treated patients[1,6,22] (Table 2).

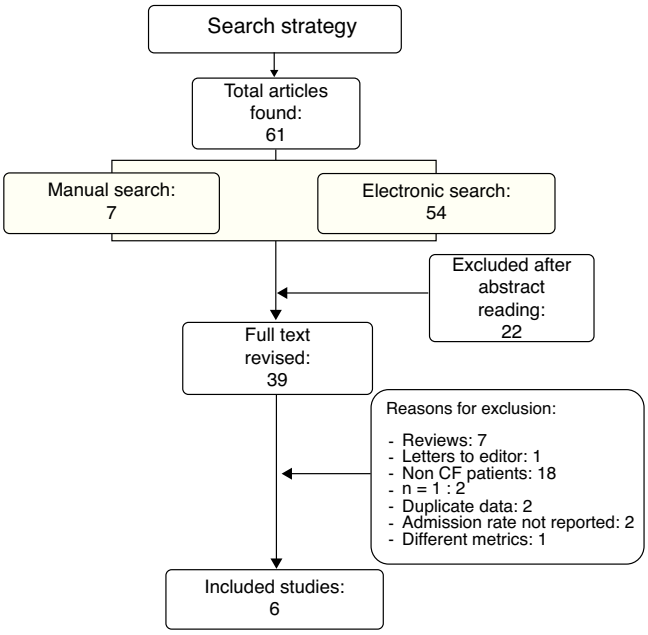

Figure 1 Search strategy flow diagram.

Efficacy of palivizumab

The six included studies reported on the rate of hospital admissions due to RSV infections. The total number of patients who received palivizumab was 354 and the admission rate among them was 0.018 (95% CI 0.0077–0.048). The number of patients in the three studies used as external controls and in the non-treated groups from three of the five included studies added up to 463 patients and showed an admission rate of 0.126 (95% CI 0.086–0.182). Heterogeneity (I^2) was moderate in the non-treated group of patients (50.6%) while it was very low (0%) in the treated group. The difference in the two admission rates was highly significant ($Q = 13.9$; $p < 0.001$) and favoured the group treated with palivizumab (Fig. 2). As a way of a sensitivity testing, when only the three studies with treated and non-treated patients were included, the weighted mean admission rate in the non-treated patients ($n = 263$) was 0.097 (95% CI 0.041–0.211) and the difference with the whole group ($n = 354$) of treated patients was also significant ($Q = 5.83$; $p = 0.016$). Furthermore, when comparing the weighted mean admission rate of the three studies used as external controls with the weighted mean admission rate of the three non-treated groups in the six selected studies, the figures were respectively 0.140 (95% CI 0.077–0.242) and 0.104 (0.052–0.199), the difference not being statistically significant ($Q = 0.43$; $p = 0.512$). Moreover, when comparing only those three studies which included treated and non-treated patients, the differences between the two groups were very close to significance ($Q = 2.49$; $p = 0.115$), the admission rate among treated patients being 0.024 (95% CI 0.005–0.098) while the one for non-treated patients being 0.093 (95% CI 0.037–0.218). Considering the whole groups of treated ($n = 354$) and non-treated patients ($n = 463$), the number necessary to treat (NNT) was nine patients.

Safety of palivizumab

Only one included study[11] showed data on the safety of palivizumab. Eighty-nine patients out of 92 who received palivizumab experienced adverse events; however, only five patients had events which were related to palivizumab prophylaxis. Nineteen of those adverse events were classified as

Table 2 Patients included in the meta-analysis.

Author	Subgroup	Admitted for RSV LRTI	Sample size
Cohen et al.[11]	Placebo control	1	94
	Palivizumab	1	92
Giebels et al.[18]	Non-treated	7	40
	Palivizumab	0	35
McCormick et al.[15]	Non-treated	15	129
	Palivizumab	1	14
Sorrentino et al.[19]	Palivizumab	0	5
Speer et al.[20]	Palivizumab	0	91
Paes et al.[21]	Palivizumab	1	117
Abman et al.[1]	External control	7	48
Armstrong et al.[6]	External control	8	80
Kristensen et al.[22]	External control	13	72

being severe, and none of them were related to palivizumab prophylaxis.

Discussion

With the data currently available, this review and meta-analysis have found that prophylactic treatment with palivizumab in patients with CF during the RSV season might be effective in reducing hospital admission rates due to infection of the lower respiratory tract by RSV. However, we could not obtain data about the effect of prophylaxis with palivizumab in other important outcomes such as mortality, severity of infection or rate of post-bronchiolitis *P. aeruginosa* colonisation.

The available data demonstrate that RSV infection in CF infants may cause significant pulmonary morbidity; prolonged hospitalisation; and complications such as mechanical ventilation, persistent hypoxaemia, and decreased lung function for several months after a lower respiratory tract infection (LRTI).[1,2] Comparing outcomes of RSV infection in eight children with BPD out of 159 total children with pre-existing lung disorders (BPD, cystic fibrosis, recurrent aspiration pneumonitis, pulmonary malformation, neurogenic disorders interfering with pulmonary mucus circulation, tracheo-oesophageal fistula, and others) before developing an RSV LRTI, there were no significant differences among seven different groups for several morbidity measures such as duration of hospitalisation, ICU admission, duration of ICU stay, mechanical ventilation and its duration.[3] The most important risk factor was lung disease severity: patients using home oxygen were more likely to be admitted to the ICU than those who had never used it. Authors concluded that children with other underlying diseases, including CF, have similar morbidity to those with BPD, and that prophylactic interventions against RSV should also be studied in these groups.[3] The fact that a LRTI caused by RSV increases the risk of being colonised by *P. aeruginosa*[5–7] is essential to evaluate the importance of RSV infections in patients suffering from CF, as it has been extensively shown that lung function deteriorates significantly after colonisation by this bacterium. From this point of view, preventing RSV infection could also mean preventing *P. aeruginosa* colonisation.

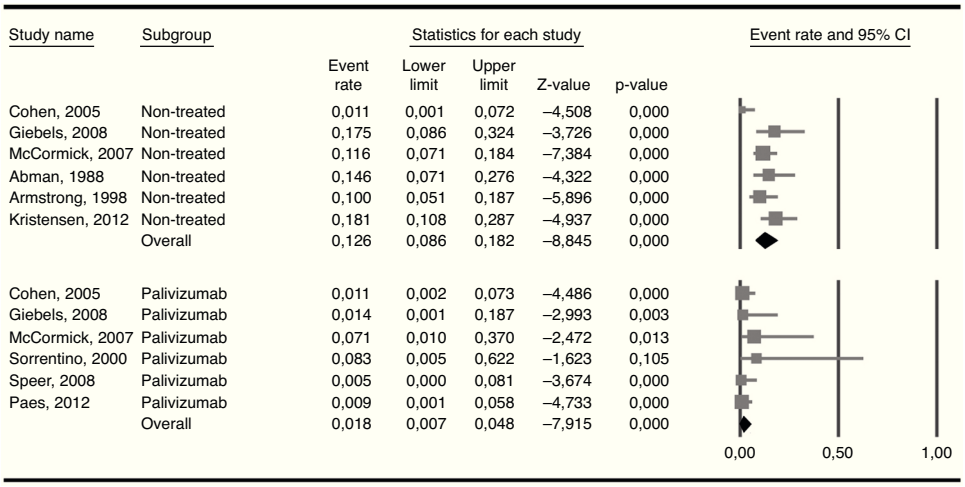

Figure 2 Admission rates in the group of patients treated with palivizumab and in the non-treated group. The difference between the overall admission rates in each group (0.126 vs. 0.018) was statistically significant (Q-test for heterogeneity: 13.9; $p < 0.001$). Heterogeneity (I^2) was 0% in the treated and 50.6% in the non-treated patients.

Taking those considerations into account, it is understandable that many CF units frequently recommend RSV prophylaxis,[15,16] even in the absence of clear evidence supporting the use of palivizumab in CF patients.

Our results are apparently contradictory to those from the only controlled clinical trial performed to date[11] which did not find any difference in the admission rates in the treated group as compared with the control group. The reasons for these contradictory results may be diverse. For instance, clinical trials entail closer observation of patients, which usually translates into faster interventions than in the general population, thus probably lowering the hospital admission rates both in the intervention and in the control groups, thereby making it very difficult to find differences when groups are relatively small. In contrast with the identical admission rates in the active and control groups, the study found that the proportion of patients who tested positive for RSV antigen was 13% in the active group and almost double that in the control group (23%). In a real-life setting this substantial difference might have implied a higher rate of hospital admissions in the group with a higher rate of positive tests, i.e. in the non-treated group.

A quite recent study[23] performed in a very large population of CF children, exposed and non-exposed to palivizumab, conducted in the USA and focused in the incidence of hospitalisations due to RSV (and also to all LRTI in a broader sense) found that RSV-related hospitalisations – which is the main interest in this case – were lower, albeit not significantly, in the group exposed to palivizumab (hazard ratio 0.57; 95% CI 0.20–1.60). The authors concluded that the incidence rates suggested potentially positive effects of palivizumab, but the results were not conclusive due to the small event rate (32 RSV-related hospitalisations). Unfortunately, we could not include this study in the present meta-analysis as the metrics were different from the rest of the studies of interest.

The main limitation of the present meta-analysis is that it includes studies which were not proper controlled clinical trials, i.e. they did not include a randomised control group and there was not consistent blinding. As already stated, only one study was a properly randomised placebo-controlled clinical trial and in fact, the Cochrane reviews[12–14] on this topic had reported this, and had suggested the need for more studies in order to clarify the usefulness of palivizumab prophylaxis in CF patients.

The results of the present meta-analysis cannot indicate beyond doubt that palivizumab prophylaxis in CF patients actually reduces the admission rates due to RSV infections, but suggests that there is an urgent need for new clinical trials which definitively clarify the efficacy and safety of palivizumab in those patients. In fact, these results suggest that there might be a role of this drug in the prevention of severe lower airway infection by RSV in CF patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Abman SH, Ogle JW, Butler-Simon N, Rumack CM, Accurso FJ. Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. J Pediatr. 1988;113:826–30.
2. Hiatt PW, Grace SC, Kozinetz CA, Raboudi SH, Treece DG, Taber LH, et al. Effects of viral lower respiratory tract infection on lung function in infants with cystic fibrosis. Pediatrics. 1999;103:619–26.
3. Arnold SR, Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, et al. Variable morbidity of respiratory syncytial virus infection in patients with underlying lung disease: a review of the PICNIC RSV database pediatric investigators collaborative network on infections in Canada. Pediatr Infect Dis J. 1999;18:866–9.
4. Petersen NT, Hoiby N, Mordhorst CH, Lind K, Flensborg EW, Bruun B. Respiratory infections in cystic fibrosis patients caused by virus, chlamydia and mycoplasma – possible synergism with *Pseudomonas aeruginosa*. Acta Paediatr Scand. 1981;70:623–8.
5. Collinson J, Nicholson KG, Cancio E, Ashman J, Ireland DC, Hammersley V, et al. Effects of upper respiratory tract infections in patients with cystic fibrosis. Thorax. 1996;51:1115–22.
6. Armstrong D, Grimwood K, Carlin JB, Carzino R, Hull J, Olinsky A, et al. Severe viral respiratory infections in infants with cystic fibrosis. Pediatr Pulmonol. 1998;26:371–9.
7. Van Ewijk BE, Wolfs TF, Aerts PC, Van Kessel KP, Fleer A, Kimpen JL, et al. RSV mediates *Pseudomonas aeruginosa* binding to cystic fibrosis and normal epithelial cells. Pediatr Res. 2007;61:398–403.
8. de Vrankrijker AM, Wolfs TF, Ciofu O, Hoiby N, Van der Ent CK, Poulsen SS, et al. Respiratory syncytial virus infection facilitates acute colonization of *Pseudomonas aeruginosa* in mice. J Med Virol. 2009;81:2096–103.
9. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics. 1998;102:531–7.
10. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top Jr FH, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003;143:532–40.
11. Cohen AH, Boron ML, Dingivan C. A phase IV study of the safety of SynagisTM (Palivizumab) for prophilaxis of respiratory syncytial virus. Proc Am Thorac Soc. 2005;2:A189.
12. Robinson KA, Odelola OA, Saldanha I, McKoy N. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. Cochrane Database Syst Rev. 2010;2:CD007743.
13. Robinson KA, Odelola OA, Saldanha IJ, McKoy NA. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. Cochrane Database Syst Rev. 2012;2:CD007743.
14. Robinson KA, Odelola OA, Saldanha IJ, McKoy NA. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. Cochrane Database Syst Rev. 2013;6:CD007743.
15. McCormick J, Southern KW. A survey of palivizumab for infants with cystic fibrosis in the UK. Arch Dis Child. 2007;92:87–8.

16. Hampp C, Saidi AS, Winterstein AG. Palivizumab utilization and compliance: trends in respiratory syncytial virus prophylaxis in Florida. J Pediatr. 2010;156:953–9.
17. Giusti R. North American synagis prophylaxis survey. Pediatr Pulmonol. 2009;44:96–8.
18. Giebels K, Marcotte JE, Podoba J, Rousseau C, Denis MH, Fauvel V, et al. Prophylaxis against respiratory syncytial virus in young children with cystic fibrosis. Pediatr Pulmonol. 2008;43:169–74.
19. Sorrentino M, Powers T. Effectiveness of palivizumab: evaluation of outcomes from the 1998 to 1999 respiratory syncytial virus season. The Palivizumab Outcomes Study Group. Pediatr Infect Dis J. 2000;19:1068–71.
20. Speer ME, Fernandes CJ, Boron M, Groothuis JR. Use of palivizumab for prevention of hospitalization as a result of respiratory syncytial virus in infants with cystic fibrosis. Pediatr Infect Dis J. 2008;27:559–61.
21. Paes B, Mitchell I, Li A, Lanctot KL. Respiratory hospitalizations and respiratory syncytial virus prophylaxis in special populations. Eur J Pediatr. 2012;171:833–41.
22. Kristensen K, Hjuler T, Ravn H, Simoes EA, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis. 2012;54:810–7.
23. Winterstein AG, Eworuke E, Xu D, Schuler P. Palivizumab immunoprophylaxis effectiveness in children with cystic fibrosis. Pediatr Pulmonol. 2012, http://dx.doi.org/10.1002/ppul.22711.