Treatment of respiratory syncytial virus with palivizumab: a systematic review

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Background: **Palivizumab has proven efficacy for prophylaxis of respiratory syncytial virus (RSV) in infants with prematurity or congenital heart disease. Despite a paucity of data, palivizumab is sometimes used to prevent progression when high-risk patients present with upper respiratory tract infection (URTI) due to RSV, or as therapy when any patients present with severe lower respiratory tract infection (LRTI) caused by RSV.**

Methods: **A systematic review of the literatures on the use of palivizumab as therapy for RSV was conducted. The primary outcomes were progression from URTI to LRTI and survival rates. Secondary outcomes were adverse events due to palivizumab, serum palivizumab level, and RSV concentration in respiratory secretions.**

Results: **The search yielded 1 case report, 4 case series, and 2 randomized controlled trials (RCTs) with a total of 136 adults and children. The RCTs were not powered to look at clinical outcomes. By combining all reported clinical outcomes, 3 (12%) of 25 patients with URTI who were given palivizumab died of RSV and 5 of 88 patients with LRTI at the time of treatment died of RSV (6%). Palivizumab levels appeared to be adequate for at least 3 weeks of intravenous injection at 15 mg/kg. The therapy resulted in decreased RSV concentrations in tracheal secretions.**

Conclusion: **Larger RCTs will be required before palivizumab can be recommended as therapy for RSV in any clinical setting.**

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Introduction

Respiratory syncytial virus (RSV) causes acute upper and lower respiratory tract infection in all age groups, but severe lower respiratory tract infection primarily occurs in the elderly, severely immunocompromised patients, and in children in their first year of life.[1,2] One potential agent for treatment of severe RSV infection is palivizumab. This monoclonal antibody directed against the RSV F glycoprotein has proven efficacy in preventing RSV hospitalizations for children under 2 years of age with chronic lung disease or hemodynamically significant congenital heart disease and for those children less than 6 months of age born prior to 36 weeks gestation.[3-5] Prophylactic use of palivizumab in these high-risk groups is now accepted in many countries. It is used in infants born at 32 to 35 weeks gestation[3] with the only safety concern being rare cases of anaphylaxis.

Palivizumab has not been studied for therapy of RSV. The precursor of palivizumab for RSV prophylaxis is RSV immune globulin. This product does not decrease the duration of hospitalization or intensive care unit stay of high-risk or previously healthy children when used therapeutically.[6,7] Nonetheless, palivizumab is sometimes used when patients present with severe RSV disease or when high-risk patients present with RSV upper respiratory tract infection (URTI). The aim of this review is to summarize the published safety and efficacy data at any dose of palivizumab for RSV therapy in any patient group.

Methods

Search methods

A comprehensive search of studies on palivizumab up to August 2009 was conducted in the following electronic databases: Medline, Embase, Scopus, and the Cochrane Database of Systematic Reviews. Studies indexed after that date met the inclusion criteria were also included if the authors were aware of them. Bibliographies of key articles were also scanned. The titles and abstracts of studies identified by the search were screened for potential relevance. The full text of all potentially relevant studies was reviewed to

determine if they fulfilled the eligibility criteria.

Study identification and data extraction

Studies were included if 1) palivizumab was used in the treatment of patients with RSV infection; 2) information on patient outcomes was available; and 3) the study was published in English language. We expected that there would be few studies; therefore we chose to include studies of any design that reported on any patient outcome so long as palivizumab was used therapeutically. Citations were screened by one investigator and data from the included studies were extracted with an electronic data extraction form by one investigator and checked by a second investigator. Disagreements were resolved by consensus.

Outcomes

The primary outcomes of interest were progression from URTI to LRTI and survival rates. Secondary outcomes of interest were adverse events due to palivizumab, serum palivizumab level, and RSV concentration in respiratory secretions.

Data analysis

Meta-analysis was not appropriate in the heterogeneity of patient characteristics and there was lack of randomization in most studies. Therefore, the studies were described qualitatively.

Results

The search yielded 5319 titles of interest. Once the full articles were extracted, 6 studies from the search (Fig., Table)[8-13] and a 2009 retrospective case series identified after the initial literature search[14] were included in the present review. One study was excluded as only the abstract was in English[15] and another was excluded as it appeared to have only been published as an abstract.[16] The 7 included studies consisted of one case report, four case series, and two placebo-controlled randomized controlled trials (RCTs) (Table).

The case report was of a 56-year-old woman with respiratory failure[10] treated 15 days after a hematopoietic stem cell transplant (HSCT), who improved rapidly and was on room air 9 days later.

The earliest of the 4 case series was a phase I study to examine the use of palivizumab and ribavirin in adult and pediatric HSCT recipients.[9] The 3 patients with URTI at presentation did not progress while 2 of 12 patients with LRTI died of RSV, with none of the other 10 patients with LRTI requiring mechanical ventilation. The second case series reported the use of palivizumab and ribavirin in the treatment of 31 children having a risk factor for severe RSV disease.[12] At baseline, 18 (58%) patients had LRTI, 17 (55%) were hypoxic, 10 (32%) required intensive care unit treatment, and 5 (16%) were mechanically ventilated. Two children (6.4%) died: one was 15 days post-HSCT and the other was on chemotherapy, and both were being ventilated when they received palivizumab. Another case series included adult and pediatric HSCT recipients.[13] Nine patients with RSV URTI and 10 patients with RSV LRTI initially received palivizumab. Five of the URTI patients progressed to LRTI; 3 of these 5 but none of the 10 patients who presented with a LRTI died of RSV at 34, 78, and 87 days after RSV diagnosis. The progression rate from RSV URTI to LRTI (56%) was identical to that in 9 patients in the same center who were not treated with palivizumab, with 2 of the latter patients who died of RSV at 23 and 47 days after RSV diagnosis. The fourth case series described 23 adults with lung or heart-lung transplants, all of whom recovered on a multi-drug regimen that included palivizumab.[14] It appears that many of the RSV infections in the latter study occurred several years post-transplant; the study also included patients with parainfluenza virus and day 845 was the median day of onset.

One placebo controlled RCT conducted in 1998 investigated the use of palivizumab in children under the age of 24 months, who were mechanically ventilated for RSV with 6 of the 35 children having underlying chronic medical problems.[8] One of 18 patients in the control group died and all 17 treated patients survived. There were no statistically significant differences in survival

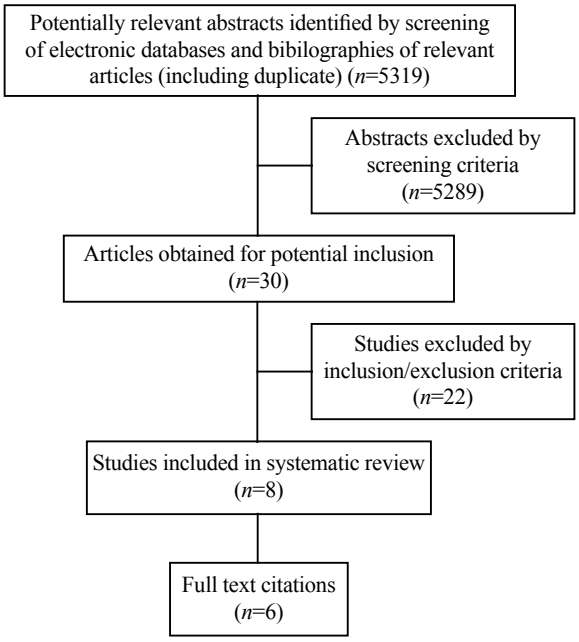

Fig. Systematic review search strategy flowchart (Liu 2009[14] was found after the initial chart review and so was not included in the flowchart).

Table Published studies of palivizumab therapy for RSV

Author, year, country	Study design	Patients	Underlying conditions	Dose*	Other therapies for RSV	Treated with URTI (did not progress/ progressed to LRTI and survived/ progressed to LRTI and died of RSV)	Treated with LRTI (survived/died of RSV)	Survivors	Adverse events in treated patients
Malley, 1998[8] USA	Placebo-controlled RCT	17 children 1.2 to 23.8 mon of age (median 3.2 mon) ventilated for RSV LRTI (another 18 received placebo)	Congenital anomalies (2), quadriplegia (1), healthy (14)	15 mg/kg	None	0	17 (17/0)	17/17 (100%)	1 patient with fever, elevated ALT level, anemia, dyspnea, and respiratory disorder (subglottic stenosis) and 2 with pneumonia
Boeckh, 2001[9] USA	Case series	15 patients 2-60 y of age; mean 36 y	HSCT within previous 3 mon	15 mg/kg	Aerosolized ribavirin (2 g/d if URTI and 6 g/d if LRTI) for 2 to 9 days (median 7 days)	3 (3/0/0)	12 (9/3)	12/15 (80%)	None
Banna, 2004[10] Italy	Case report	56-y-old woman	13 days post HSCT	8 mg/kg	Betamethasone 4 mg bid	0	1 (1/0)	1/1 (100%)	None
Saez-Llorens, 2004[11] USA/ Panama	Placebo-controlled RCT	30 children ≤24 mon of age (another 29 received placebo)	Healthy	5 mg/kg (*n*=8, mean 2.9 mon old); 15 mg/kg (*n*=22, mean 5.2 mon old)	None	0	30 (30/0)	30/30 (100%)	Respiratory failure with secondary bacterial pneumonia (*n*=1) and fever, rash and tachycardia for one day starting one day post-infusion (*n*=1)
Chavez-Bueno, 2007[12] USA	Case series	31 children aged 1 wk to 16.8 y (median 23.4 mon)	Malignancy (11), transplant (7), CHD (4), prematurity (5), RSV myocarditis (2), treacher collins (1), healthy (1)	Mean 14.9 mg/kg†	25 received ribavirin (23 by aerosol, one intravenously, and one via both routes) for 2-15 days (median 4 days)	13 (NR)	18 (16/2)	29/31 (94%)	None
De Fontbrune, 2007[13] France	Case series	8 children ≤15 y of age and 11 older (range 5-63 y)	HSCT with RSV from 33 days prior to 300 days post-transplant (12 for leukemia, 2 for lymphoma/ myeloma, 2 for non-malignancies)	15 mg/kg with up to 3 doses per mon if still ill (median 1 dose)	None	9 (4/2/3)	10 (10/0)	16/19 (84%)	NR
Liu, 2009[14] USA	Case series	23 adults	Lung or heart-lung transplant recipients	15 mg/kg	Aerosolized ribavirin 6 g/d, 0.5 mg/kg IVIG, methylprednisolone 500 mg daily for 3 days	NR	NR	23/23 (100%)	NR
Total		136				25 (7/2/3)‡,§	88 (83/5)§	91/136 (67%)	

RSV: respiratory syncytial virus; CHD: congenital heart disease; HSCT: hematopoietic stem cell transplant; IVIG: intravenous immune globulin; LRTI: lower respiratory tract infection; NR: not reported; RCT: randomized controlled trial; URTI: upper respiratory tract infection. *: All doses given intravenously; †: Two children received a second dose 3 and 5 days later; ‡: Thirteen of the patients survived but it was not stated if they developed LRTI (Chavez); §: For 23 other patients, it was not reported if they had URTI or LRTI when treated.[14]

or in days of hospitalization, mechanical ventilation, or supplemental oxygen use in the two groups, but the study was not adequately powered for clinical outcomes. This study plus one other study[11] measured serum palivizumab levels 30 days after therapy of RSV at a dose of 15 mg/kg with a mean of 34.9[8] and 38.4[11] μg/mL. The concentration of RSV 1 and 2 days after therapy was significantly lower in the treatment group in tracheal secretions but not in nasal aspirates in the single study.[8] The second placebo-controlled RCT conducted in 2004 was a phase I/II study in previously well children under the age of 24 months who met the inclusion criteria including hospitalization for RSV LRTI for less than 72 hours and over 30% supplemental oxygen.[11] One of 29 placebo-controlled patients died and all 30 treated patients survived. Again, there were no statistically significant differences in survival or in hospital course, but the study was powered to look at serum palivizumab levels rather than efficacy. The patients usually received a single intravenous dose of palivizumab (15 mg/kg) (Table), equivalent to the standard intramuscular dose used monthly for routine prophylaxis. Palivizumab was generally well-tolerated with no serious adverse events being clearly drug-related (Table).

Discussion

Seven studies published between 2001 and 2010 met the inclusion criteria for this systematic review of the therapeutic use of palivizumab. When used for prophylaxis, the drug was generally well tolerated. The concentration of RSV in tracheal secretions was shown to decrease in treated ventilated children versus a control group in the only study that measured this parameter.[8] In the two studies that reported them, palivizumab levels were close to the threshold associated with significant anti-RSV activity in an animal model (40 μg/mL) 4 weeks after infusion[8,11] and similar to the mean trough level in infants prior to the second dose of palivizumab when used for prophylaxis (37 μg/mL).[4] This long duration of activity may be particularly important in the severely immunocompromised host where prolonged shedding is the norm.[17]

Combining all 7 case reports, case series and prospective studies, 3 of 25 patients treated with palivizumab had only URTI and eventually died of RSV (12%); whereas 5 of 88 patients with LRTI died (6%) during treatment.[14] Assessment of the efficacy of palivizumab in preventing progression of RSV is complicated because the natural history of RSV URTI in patients at risk for severe disease is not fully delineated. Young children at the highest risk of severe RSV infection on the basis of prematurity, chronic lung disease, or congenital heart disease are usually treated preventively with palivizumab if they live in a country where palivizumab is available.[3] Since there are no RCTs of palivizumab in immunocompromised hosts, guidelines are typically permissive but not prescriptive.[3] Therefore, treatment of RSV URTI with palivizumab to prevent progression has been studied in severely immunocompromised hosts who are not qualified for prophylaxis. In this review, 5 of 12 HSCT recipients (42%) progressed to LRTI after the treatment of URTI with palivizumab and 3 of these patients (25%) died of RSV infection. One could compare this with a study of 122 HSCT recipients with weekly nasopharyngeal samples for the first 100 days post-transplant. This group had 5 RSV infections (20%) with only one progressing to LRTI.[18] A similar study was performed in 2764 HSCT recipients who had testing done when they were symptomatic in the first 100 days post-transplant, resulting in 44 diagnoses of RSV, of which 12 (27%) progressed to LRTI. Two patients required ventilation and both survived.[19] However, it is not mentioned in these two studies if any of the patients with RSV received palivizumab as therapy. It is likely that RSV diagnosed via weekly surveillance[18] would be less severe than the RSV URTI treated with palivizumab in the studies (Table), where testing was presumably based on symptoms and therapy provided only to the highest risk patients. Clearly it would be helpful to collect further data on the natural history of RSV URTI in patients with different ages and degrees of immunosuppression. In those at the highest risk, a RCT of palivizumab versus placebo in the treatment of RSV needs to be performed, presumably with a one-time dose of 15 mg/kg. If palivizumab can be shown to prevent progression of RSV URTI to LRTI, the next challenge will be devising a system for testing the highest risk patients for RSV URTI and arranging prompt treatment with palivizumab.

Similarly, the literature on palivizumab for therapy of severe RSV disease is immature. In this review, 5 of 88 patients who were given palivizumab for RSV LRTI (6%) died. However, this is complex to interpret as patients varied from previously well young children requiring oxygen to severely immunocompromised children already with mechanical ventilation.

Palivizumab is a product which has controversial cost-effectiveness for prophylaxis.[20] Treatment of RSV would presumably usually require only one dose, but costs would be very high in older children and adults (approximately $288 US/kg body weight to administer 15 mg/kg), with cost-effectiveness obviously depending on the averted morbidity and mortality. Despite the cost, some clinicians may consider palivizumab for a patient requiring intensive care for RSV given the currently available data, particularly among the highest risk patients (such as recent transplant recipients or young children with severe cardiac or pulmonary disease). However, RCTs powered to look at clinical outcomes are clearly required before such therapy can be justified.

Motavizumab is a higher titer version of palivizumab.[21] In the only study published to date describing use of this agent for therapy of RSV, 31 previously well children of less than 24 months of age admitted to the hospital with RSV LRTI in Chile and the USA were randomized to receive placebo versus motavizumab and viral shedding was shown to be decreased in the children treated with motavizumab starting one day after therapy.[21] Motavizumab has not yet been approved for RSV prophylaxis in the United States because of concerns regarding a possible higher incidence of hypersensitivity reactions.[22] It is therefore debatable if further studies of RSV monoclonal antibodies as RSV therapy should be conducted with palivizumab or motavizumab.

The primary limitation of the current review is that the successes and failures with palivizumab in therapy of RSV were not reported. Clinicians are more likely to report successes other than failures. Combining pooled data from heterogeneous populations can result in bias in reporting. A further limitation is that foreign

language publications were excluded.

In conclusion, RCTs with sufficient power are needed to assess the efficacy of palivizumab in preventing progression of RSV URTI and in treating severe RSV infection. Until such studies are performed, palivizumab remains a very expensive therapy with no proven efficacy.

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Contributors: Robinson JL designed the study. Hu J did the literature review. Both authors verified all data. Hu J wrote the first draft of the manuscript.

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