BRIEF REPORT

Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children

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Citation
al-Alaiyan S, Pollack P, Notario GF. Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children. Drugs in Context 2015; 4: 212270. doi: 10.7573/dic.212270

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Article URL
http://www.drugsincontext.com/safety-pharmacokinetics-extended-use-palivizumab-saudi-arabian-infants-children

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Provenance
Submitted, peer-reviewed externally

Dates
Submitted: 26 November 2014
Revised manuscript submitted: 4 February 2015
Accepted for publication: 6 February 2015
Publication date: 27 February 2015

Publisher and contact information
Drugs in Context is published by Just Medical Media Ltd Undermount, Rydal, Ambleside, Cumbria, LA22 9LT, UK ISSN 1740-4398
Just Medical Media Limited is registered in England Number 6891187 VAT GB 945 1713 22
Julia Savory
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Abbreviations
AE, adverse event; CLDP, chronic lung disease of prematurity; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus
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**Abstract**

**Background:** The peak season of respiratory syncytial virus (RSV) infections in warmer climates may extend beyond the typical five-month RSV season of temperate regions. Additional monthly doses of palivizumab may be necessary in warmer regions to protect children at high risk for serious infection by the RSV.

**Methods:** In a Phase II, single-arm, single-center, non-comparative, open-label, prospective study conducted in Saudi Arabia, children at high risk for RSV infection received up to seven monthly injections of palivizumab (15 mg/kg) during the 2000–2001 RSV season. Key enrollment criteria were no previous exposure to palivizumab and gestational age ≤35 weeks, ≤6 months of age at enrollment, or chronic lung disease and ≤24 months of age at enrollment. We wished to assess the safety, immunogenicity, and pharmacokinetics of palivizumab as an extended seven-dose regimen.

**Results:** Of 18 enrolled patients, 17 patients received seven palivizumab injections. Seven adverse events (AEs) occurred in five patients. Bronchiolitis was the most commonly reported AE. Six serious AEs occurred in four patients. No AEs were considered related to palivizumab. Trough levels of palivizumab in serum were >40 μg/mL in most patients after the first injection and in 16/18 and 14/17 patients after the fourth and sixth injections, respectively. Except for one patient at one visit, the anti-palivizumab titer was <1:10 at all visits.

**Conclusion:** These data suggest that an extended palivizumab regimen of up to seven monthly doses during the RSV season exhibited an acceptable safety profile in children at high risk for RSV infection in Saudi Arabia.

**Keywords:** infants, open-label, palivizumab, pediatrics, pharmacokinetics, respiratory syncytial virus, safety, Saudi Arabia.

**Introduction**

Most children have experienced at least one infection with the respiratory syncytial virus (RSV) by 2 years of age [1,2]. Because of the high prevalence of RSV infections, more serious cases leading to hospitalization and intensive medical treatment incur a substantial economic burden on families and healthcare systems [3,4].

Risk factors for serious infection with RSV include: preterm birth; chronic lung disease of prematurity (CLDP; also known as bronchopulmonary dysplasia); cyanotic or complicated congenital heart disease; and immunodeficiency disease or immunosuppression caused by therapy [5–7]. Children born preterm who attend daycare or who live in a household with one or more siblings younger than 5 years of age are at a higher risk of contracting serious RSV infections [8].

Additional factors that may predispose preterm children to more serious infections include low weight upon hospital admission and exposure to tobacco smoke [9]. Infants born preterm with CLDP are at a higher risk of developing RSV-associated pneumonia if they are part of a multiparous birth [10].

Despite identification of these distinct risk factors, a study conducted in the USA (N=919) showed that most RSV-infected children who had been hospitalized for respiratory infection had been healthy and without any risk factors before study entry. This finding suggested that even children without an obvious risk factor may be vulnerable to serious infection by the RSV [11].

No vaccine has been approved for the prevention of RSV infection. Prophylactic treatment with the virus-neutralizing
by the International Conference on Harmonisation, and all applicable local and federal regulations (including regulations of the government of Saudi Arabia, the King Faisal Specialist Hospital and Research Centre and its Research Advisory Council, and Good Clinical Practice guidelines). Before enrollment, written informed consent was obtained from the patient’s parent/legal guardian. As part of ethics approval, the sponsor was required to submit a final report within one year of approval and to inform the Office of Research Affairs of: proposal amendments; study termination; serious or unexpected adverse events (AEs); or any event or new information that could possibly affect the benefit–risk ratio of the study.

Patients
The study was limited to children who had never received palivizumab and who were judged by the investigator to be at risk for RSV infection and eligible to receive palivizumab. Pertinent inclusion and exclusion criteria are presented as online supplementary material. which is published here: http://www.drugsincontext.com/wp-content/uploads/2015/02/Palivizumab-in-Saudi-Arabian-children-supplementary-material.docx

Study product
Abbott Laboratories (North Chicago, IL, USA) provided vials containing palivizumab (100 mg) as sterile lyophilized monoclonal antibody, 50 mM histidine, 3.2 mM glycine, and 6% (w/v) mannitol. Palivizumab was stored at 2–8°C and was reconstituted with 1.0 mL of sterile water for injection at a final concentration of 100 mg/mL of palivizumab at pH 6.0. The solution was allowed to sit for 20 min to clarify and was used <3 h after reconstitution.

Palivizumab (100 mg/mL) was administered to patients at 15 mg/kg based on the patient’s weight at each study visit, which occurred every 25–30 days after the date of the first dose. Palivizumab was administered via intramuscular injection in the anterolateral aspect of the thigh.

Study assessments
The primary objectives of the study were to determine the safety, tolerance, and pharmacokinetics of an extended number of palivizumab injections over seven months, as well as to evaluate the generation of antibodies to palivizumab in that time frame. Safety parameters included AEs and vital signs.

A complete medical history and relevant patient demographics (including possible risk factors for serious RSV infection) were obtained at the first study visit. At each study visit, safety and tolerance were monitored. A complete physical examination (vital signs, weight, height, chest examination) was undertaken, and information was collected regarding AEs (including intercurrent illness, concomitant medications, and hospitalizations). On days when the study drug was

Methods
Study design
This was a Phase II, single-arm, open-label, non-comparative, prospective study in which palivizumab (15 mg/kg) was administered to children approximately every 30 days at a single site in Riyadh, Saudi Arabia. Patients meeting the inclusion criteria received ≤7 doses during the 2000–2001 RSV season.

The study was approved by the King Faisal Specialist Hospital and Research Centre Office of Research Affairs as the independent ethics committee. The study was conducted in accordance with the Declaration of Helsinki, guidelines set

*Synagis; MedImmune LLC, Gaithersburg, MD, USA; AbbVie Inc., North Chicago, IL, USA.
administered, vital signs were recorded immediately before and 30 min after administration. Study investigators maintained telephone contact with the parents/legal guardians between study visits every 1–2 weeks. Parents/legal guardians were to call study personnel to report abnormalities during study visit intervals and to bring the child to the study site if medical evaluation was necessary (if time permitted). Serious AEs were those that resulted in: death; risk of death at the time of the event; inpatient hospitalization; or development of a persistent or significant disability/incapacity. Any patient hospitalized with a respiratory illness had a nasopharyngeal aspirate, wash, or swab tested for the presence of RSV antigens using the TESTPACK RSV* kit. Blood samples for testing of pharmacokinetics and immunogenicity were obtained at the first, second, fifth, and seventh visits before palivizumab administration for analyses of trough levels of palivizumab in serum and anti-palivizumab antibodies as described previously [27].

Statistical analyses

A sample size of 25 patients was considered to be sufficient to evaluate the study objectives. Power analyses were not undertaken at the time of planning the study. For one event (e.g., RSV infection) in 25 subjects (event rate of 4%), the corresponding 95% confidence interval (CI) would have been from 0.1% to 20.4%. For one event in 18 subjects, the corresponding 95% CI would be from 0.1% to 27.3%.

All enrolled patients who received ≥1 dose of palivizumab were included in the analyses (intention-to-treat). Because of the small sample size and occurrence of only one RSV-positive hospitalization, planned statistical analyses were not carried out. Baseline characteristics, safety, pharmacokinetics, and immunogenicity were summarized using mean, standard error, median, and range for continuous variables, and using frequency and percentage for categorical variables.

Results

Study patients and disposition

Due to a lack of patient availability, only 18 patients were enrolled in the study. The complete set of seven monthly doses of palivizumab was received by 17 patients (94.4%). The remaining patient received five doses and discontinued the study owing to infection (Figure 1). Median age of patients at enrollment was 14 (range, newborn–29) weeks. Median weight of patients at enrollment was 2.2 (range, 1.6–5.6) kg. Most patients were female (n=12 [66.7%]) and Caucasian (n=17 [94.4%]).

Table 1 lists the possible risk factors for RSV infection among patients. Most patients were part of multiparous births. Median gestational age at birth was 28 weeks and the median weight at birth was 0.98 kg. Four patients had CLDP. For patients who did not have CLDP, the initial risk factor was gestational age at birth ≤35 weeks and being ≤6 months of age at the time of enrollment per inclusion criteria. Six patients lived in a household with one person who smoked but all patients lived in households in which the primary caregiver did not smoke. Only one patient attended daycare and no patient had siblings in daycare.

Table 1. Risk factors for infection by the respiratory syncytial virus (N=18).

| Risk factor                          | n (%) |
|--------------------------------------|-------|
| Multiple birth status                |       |
| Single                               | 6 (33.3) |
| Twin                                 | 3 (16.7) |
| Triplet or greater                   | 9 (50.0) |
| Birth order                          |       |
| 1                                    | 12 (66.7) |
| 2                                    | 4 (22.2)  |
| 3                                    | 2 (11.1)  |
| Number of smokers in household       |       |
| None                                 | 12 (66.7) |
| 1                                    | 6 (33.3)  |
| ≥2                                   | 0       |
| Does the primary caregiver smoke?    |       |
| Yes                                  | 0       |
| No                                   | 18 (100.0) |
| Is the patient in daycare?           |       |
| Yes                                  | 1 (5.6)  |
| No                                   | 17 (94.4) |

(Continued)
AEs

Five patients (27.8%) experienced ≥1 AE during the study (total number of AEs was seven; Table 2). The most frequently reported AE was bronchiolitis. No deaths occurred during the study. One of the seven AEs (melena) was not considered serious and occurred between the third and fourth months of treatment. The other six AEs, reported in four patients, were considered serious. Two of these patients were hospitalized once each for bronchiolitis, both of whom tested negative for RSV infection at that time; both AEs occurred between the fourth and fifth months of treatment. The third patient was hospitalized twice, once for a chest infection and CLDP, and once for CLDP and bronchopneumonia; both AEs occurred between the third and fourth months of treatment. RSV testing for this patient was negative during the hospitalization for chest infection and CLDP and was not performed during the hospitalization for CLDP and bronchopneumonia. The fourth patient was also hospitalized twice: once for bronchiolitis and once for a chest infection that was classified as a “medically important event.” The patient tested positive for RSV infection during hospitalization for bronchiolitis, tested negative during hospitalization for chest infection and, ultimately, was withdrawn from the study during the fifth month of treatment. All AEs were considered by the investigator to be not related or probably not related to the study drug. Data on respiratory-related hospitalization are presented in Table 3.

Pharmacokinetics and immunogenicity

The mean (± standard deviation) trough concentration of palivizumab in serum was 44.72 μg/mL (18.67 μg/mL) after the first dose, a level considered to be protective in the cotton-rat model [27].

### Table 1. Risk factors for infection by the respiratory syncytial virus (N=18) (continued).

| Risk factor                                      | n (%)     |
|--------------------------------------------------|-----------|
| Number of siblings in daycare                    | 0         |
| Number of people living in the household<sup>a</sup> |           |
| 3                                                | 4 (22.2)  |
| 6                                                | 4 (22.2)  |
| 7                                                | 1 (5.6)   |
| 9                                                | 1 (5.6)   |
| 10                                               | 6 (33.3)  |
| 11                                               | 2 (11.1)  |
| Number of siblings living in the household<sup>a</sup> |           |
| 0                                                | 4 (22.2)  |
| 2                                                | 5 (27.8)  |
| 3                                                | 3 (16.7)  |
| 6                                                | 1 (5.6)   |
| 7                                                | 1 (5.6)   |
| 8                                                | 4 (22.2)  |
| Supplemental oxygen required?                     |           |
| Yes                                              | 1 (5.6)   |
| No                                               | 17 (94.4) |
| Chronic lung disease<sup>b</sup>                  |           |
| Yes                                              | 4 (22.2)  |
| No                                               | 14 (77.8) |
| Gestational age at birth, wk<sup>b</sup>          | 27.9 (23–34) |
| Birth weight, kg<sup>b</sup>                      | 0.98 (0.44–2.22) |

<sup>a</sup>Study patient not included in the number of people living in the household.

<sup>b</sup>Median (range).

### Table 2. Adverse events (N=18).

| Body system            | Severity | Relationship to study drug |
|------------------------|----------|-----------------------------|
| COSTART term           | Total (%)| Mild | Moderate | Severe | Not | Probably Not | Possibly | Probably |
| Total patients<sup>a</sup> ≥1 AE | 5 (28) | 2  | 1  | 2  | 4  | 1  | 0  | 0  |
| Body as a whole<sup>b</sup> Infection | 2 (11) | 0  | 1  | 1  | 2  | 0  | 0  | 0  |
| Digestive system       | Melena   | 1 (6) | 1  | 0  | 0  | 1  | 0  | 0  |
| Respiratory system<sup>b</sup> Bronchiolitis | 3 (17) | 1  | 1  | 1  | 3  | 0  | 0  | 0  |
| Lung disorder          | Pneumonia | 1 (6) | 0  | 0  | 1  | 1  | 0  | 0  |

<sup>a</sup>Two patients experienced two events each; one event was categorized under two body systems (lung disorder and infection) per medical decision. Thus, the total number of events shown (n=8) exceeds the total number of actual events (n=7) and the total number of patients (n=5) who experienced AEs.

<sup>b</sup>Serious AE.

AE, adverse event.
in serum rose between visits five and seven, but the difference between these two values was not significant. Anti-palivizumab titers were <1:10 in all patients at all visits except for one patient who had a titer of 1:20 at the second visit. This patient’s titer was <1:10 at visits five and seven.

### Discussion

The present study provides evidence that seven monthly doses of palivizumab were well tolerated by pediatric patients at high risk of serious respiratory disease caused by the RSV. All serum levels of palivizumab were within the range of those observed in previous palivizumab studies, and were correlated with protection [12,27,28]. This is the first prospective study examining this number of palivizumab injections in this population (though a retrospective global study also showed that >5 doses were well tolerated by infants) [29]. Patients in pivotal studies of palivizumab had only received ≤5 injections [2,28]. In addition to a recent study in Taiwan showing the effectiveness of six doses of palivizumab in preventing RSV hospitalization in 127 infants born prematurely or with CLDP [30], the results reported here have particular relevance for those regions in which cases of RSV occur outside of the five-month season that is typical in areas with temperate climates. In countries such as Saudi Arabia, additional doses of palivizumab beyond the five-dose regimen recommended by the American Academy of Pediatrics may be necessary to provide added protection for vulnerable members of the pediatric population during extended periods of widespread RSV activity. Palivizumab exhibited an acceptable safety profile in patients receiving seven injections, with no evidence of a substantial antibody response to the study drug. The AEs that occurred were nearly all related to the respiratory system and were typical of those seen commonly in the high-risk population of patients treated in this study.

The RSV is a major cause of respiratory infections among infants and young children in Middle East countries [26,31–33]. In Saudi Arabia, the RSV can be the cause of ≤83% of all LRTIs in infants and young children of infants and young children in Middle East countries [26,31–33]. Studies in Jordan, Qatar, and Saudi Arabia have shown that the peak season of RSV infection occurs in the winter months, with the highest number of infections reported between December and February [24,31,32]. However, in Saudi Arabia and Qatar, cases have been detected beyond the time of the “typical” RSV season [24–26,32].

Cases of RSV infection have also been reported throughout the year in other countries with warmer climates, though ambient humidity and rainfall have been proposed to have an effect on infection rates [17,34,35]. A survey of five North American cities demonstrated a bimodal relationship between temperature and RSV infections, as well as a direct relationship to relative humidity [35]. Peak RSV activity in Riyadh occurs in late autumn and early winter at a time when temperatures are relatively mild (14–21°C) but humidity levels are relatively high (36–47%) [23,35,36]. Similarly, in Jordan, the prevalence of RSV infection is higher at times of lower temperatures and higher humidity [31]. Lower levels of humidity during other times of the year may mitigate (but not totally eliminate) the number of RSV infections because cases have been reported outside of the peak season [24,25]. Therefore, meteorologic variables may be

| Table 3. Respiratory-related hospitalizations (N=18). |
|-----------------------------------------------------|
| **n (%)**                                           |
| Number of patients hospitalized<sup>a,b</sup>        | 4 (22.2) |
| Number of hospitalizations<sup>a,b</sup>            | 5 (27.8) |
| Hospitalizations<sup>a,c</sup>                      |
| Outpatient admissions                                | 3 (60.0) |
| Emergency admissions                                | 2 (40.0) |
| Admission to the intensive care unit                | 0        |
| Length of hospital stay, days                       | –        |
| RSV status<sup>a,d</sup>                            |
| Number of RSV-negative patients                     | 3 (16.7) |
| Number of RSV-positive patients                     | 1 (5.6)  |
| Primary diagnosis<sup>a,c</sup>                     |
| Number of upper respiratory tract infections        | 0        |
| Number of lower respiratory tract infections        | 5 (100.0)|
| Supplemental oxygen<sup>a,c</sup>                   |
| Not required                                        | 1 (20.0) |
| Oxygen required                                     | 4 (80.0) |
| Days of oxygen required                             | –        |
| Maximum daily requirement, L/min                    | –        |
| Mechanical ventilation<sup>a,c</sup>                |
| Not required                                        | 2 (60.0) |
| Required                                            | 3 (40.0) |

<sup>a</sup>One patient was hospitalized twice, so the number of hospitalizations exceeds the number of hospitalized patients.

<sup>b</sup>Percentage of total patients enrolled (N=18).

<sup>c</sup>Percentage and/or mean of total number of hospitalizations (n=5).

<sup>d</sup>One patient was hospitalized twice but was tested for RSV infection only during the first hospitalization (negative), so RSV status during the second hospitalization was not known. RSV, respiratory syncytial virus.
only among the multiple factors that influence the rate and timing of RSV infection [34].

This study was limited by the small number of patients enrolled. Furthermore, specimen collection for RSV testing was not standardized to a single method but instead allowed for collection via nasopharyngeal aspirates, washes, or swabs. Finally, no comparative placebo group was included in this study: using a placebo in these patients after palivizumab received approval would not have been ethical.

Conclusions

The timing of prophylactic administration of palivizumab to coincide with (or shortly precede) the annual RSV infection season is expected to yield the greatest clinical benefit to those patients most at risk for infection. In many parts of the world, the RSV season has been relatively well established and the recommended five-dose injection regimen is appropriate. Nevertheless, the exact timing of the RSV season is not always predictable, even within a particular country or region [16]. Moreover, in some parts of the world, the RSV season may stretch over a greater period of time, even in regions with temperate climates [37]. In such regions, additional doses of palivizumab may be necessary to adequately protect children in high-risk groups. The data on safety and immunogenicity noted in this report provide evidence that a regimen of up to seven doses of palivizumab exhibits an acceptable safety profile in these individuals. However, further studies with a larger sample size and randomized with an ethically suitable comparative arm are required to confirm these findings.

Contributions

SA participated in the conception and design of the study as well as the acquisition, analyses, and interpretation of data. PP participated in the conception and design of the study as well as the analyses and interpretation of data. GFN participated in the analyses and interpretation of data. All authors helped to draft the manuscript and approved the final version of the manuscript.

Potential conflicts of interest

The International Committee of Medical Journal Editors’ (ICMJE) Potential Conflicts of Interests forms for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2015/02/dic.212270-COI.pdf

SA declares no conflict of interest. PP is a former employee and GFN is a current employee of AbbVie Inc., and may hold stock or options of this organization.

Funding declaration

This work was supported by AbbVie Inc., North Chicago, IL, USA.

Acknowledgments

The authors thank Jessie R Groothuis, MD, for her contributions to this manuscript, as well as the investigators, study-site staff, and patients who participated in the study. This study was conducted, analyzed, and supported by AbbVie Inc. Medical-writing support was provided by Daniel McCallus, PhD, at Complete Publication Solutions, LLC; this support was funded by AbbVie Inc. Portions of these data were presented in a poster entitled “The safety and tolerance of palivizumab in Saudi Arabian infants and children with or without chronic lung disease (CLD)” at the XIII International Symposium on Respiratory Viral Infections, Rome, Italy, 13–16 March 2011.

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Palivizumab in Saudi Arabian children

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ISSN: 1740-4398

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