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Palivizumab

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Contents

Abstract

▲ The humanised monoclonal antibody palivizumab has been developed for prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants at high risk; RSV is the most common cause of lower respiratory tract infections in infants.

▲ Palivizumab specifically inhibits an epitope at the A antigenic site of the F protein of RSV subtypes A and B. RSV replication was inhibited in nasal and tracheal aspirates from infants receiving palivizumab 15 mg/kg.

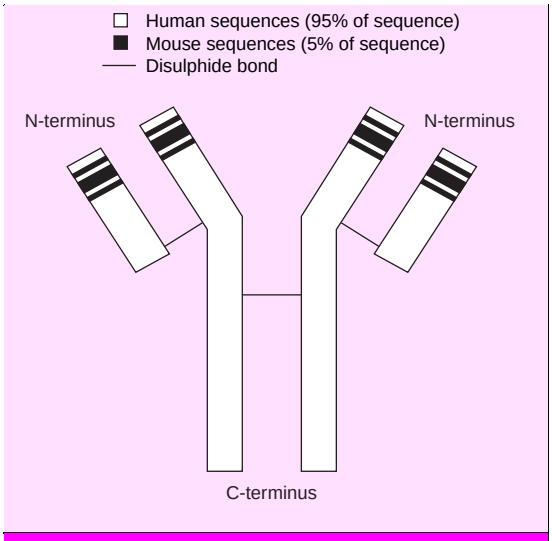
▲ Mean 30-day trough serum concentrations of palivizumab were consistently about 70 mg/L in infants receiving repeated intramuscular or intravenous palivizumab 15 mg/kg. This is above the target serum concentration of 40 mg/L estimated to reduce pulmonary RSV replication by >99% in animal studies.

▲ In a large multicentre trial in 1502 infants at high risk of RSV infection, intramuscular palivizumab 15 mg/kg more than halved the incidence of RSV-attributable hospitalisation to 4.8% compared with 10.6% in placebo recipients.

▲ In the same group of high-risk infants, palivizumab significantly decreased total days in hospital attributable to RSV infection, days with increased supplemental oxygen requirement, days with moderate to severe lower respiratory tract infections and the incidence of admissions to intensive care. It had no effect on the incidence or total number of days of ventilation.

▲ Palivizumab was well tolerated during clinical trials in infants at risk of RSV infection. The incidence of adverse events was similar in placebo (10%) and palivizumab (11%) groups. Fever, irritability and injection site reaction were the most commonly reported adverse events.

Features and properties of palivizumab (MEDI-493)	
Indications	
Prevention of respiratory syncytial virus (RSV) infection in paediatric patients at high risk of RSV infection	Focus of this profile
Mechanism of action	
Inhibition of replication of RSV; direct neutralisation of virus	Humanised monoclonal antibody specific for an epitope in the A antigenic site of the F protein of RSV
Dosage and administration	
Usual dosage in clinical trials	15 mg/kg
Route of administration	Intramuscular
Frequency of administration	Monthly
Duration of course	Throughout RSV season (commencing prior to the start of the season).
Pharmacokinetic profile (after first dose intramuscular palivizumab 15 mg/kg)	
Mean 30-day trough serum concentration	49 mg/L; increases to ~70 mg/L with repeat doses
Target serum concentration estimated to reduce viral replication >99%	>40 mg/L
Area under the plasma concentration-time curve	5295
Elimination half-life	≈24 days
Adverse events in infants	
Most frequent	Fever, irritability, injection site reaction



Palivizumab: a humanised monoclonal antibody

Respiratory syncytial virus (RSV), a member of the Paramyxoviridae virus family, is the most common cause of lower respiratory tract infection in infants and young children in the developed world, and an important cause of disease in immunocompromised patients and the elderly.[1,2] RSV infections occur seasonally and are particularly prevalent during winter and early spring. Although RSV infections occur in all age groups, most serious life-threatening infections tend to occur in the first few years of life and involve lower rather than upper respiratory tract infections. Risk factors for RSV infection include: age <6 months; underlying cardiopulmonary disorders, such as bronchopulmonary dysplasia (BPD; chronic lung disease); and, in particular, prematurity (≤35 weeks' gestation).[2] RSV subtypes A and B have been isolated from humans. The two major immunogenic proteins on their surface are the G glycoprotein which allows attachment of RSV to the host cell and the F glycoprotein which allows fusion of the virus with the host cell membrane.[2]

Prevention and treatment of RSV infections have proved difficult. In the early 1960s, vaccination of infants with a formalin-inactivated RSV vaccine augmented the severity of RSV infections and pulmonary pathology after subsequent challenge the following season.[1-3] Recent evidence suggests that neutralising antibodies may be beneficial as prophylactic agents in RSV infections.[2,4,5] In 1996, a polyclonal RSV-enriched intravenous human immunoglobulin (RSV-IGIV) directed against RSV was approved in the United States for the prophylaxis of RSV infections.[5] Importantly, with this immunoprophylaxis, there was no enhancement of viral replication or associated pulmonary pathology on RSV rechallenge.[1] Recently monoclonal antibodies have been developed which are significantly more potent than RSV-IGIV, have a smaller volume, and thus, may be administered either intramuscularly or intravenously.[5,6] Palivizumab, the focus of this profile, is a humanised monoclonal IgG antibody which specifically inhibits an epitope at the A antigenic site of the F protein (a protein with 92% homology between RSV subtypes A and B).

1. Pharmacodynamic Profile

In Vitro Studies

- Palivizumab bound to RSV F protein with a dissociation constant (K_d) of 1.4 nmol/L *in vitro*.[6]
- Palivizumab effectively neutralised a broad range of clinical isolates of RSV. It neutralised over 500 clinical isolates (subtypes A and B) collected from RSV-infected infants in a multinational study[7] and 57 clinical isolates (34 subtype A and 23 subtype B) in another study.[8]
- Palivizumab was 20- to 30-fold more active than RSV-IGIV (microneutralisation titre of 1/5543) in neutralising both subtypes of RSV *in vitro*.[6] The concentration of palivizumab required to reduce viral replication by 50% (EC_{50}) versus controls for both viral subtypes was 0.1 mg/L according to the microneutralisation assay and 0.17 mg/L according to the fusion-inhibition assay compared with 2.58 and 5.25 mg/L, respectively, for RSV-IGIV.
- In *in vitro* studies, palivizumab was 4 to 5-fold more potent than felvizumab (RSHZ19), another humanised monoclonal antibody directed against the F protein of RSV, in neutralising RSV (mea-

sured by antigen binding, neutralisation and fusion-inhibition assays).[9]

Animal Studies

• In a dose-finding study in cotton rats, palivizumab 2.5 and 5 mg/kg, administered intramuscularly or intravenously, reduced replication of RSV subtypes A and B by ≥99% in the lung at day 4 after challenge; lower doses of palivizumab were less effective (fig. 1).[6] Palivizumab serum concentrations of ~30 mg/L at the time of RSV challenge were required to reduce pulmonary RSV replication by a mean of ≥99%; however, serum concentrations of >40 mg/L reduced RSV replication by >99% in all animals.

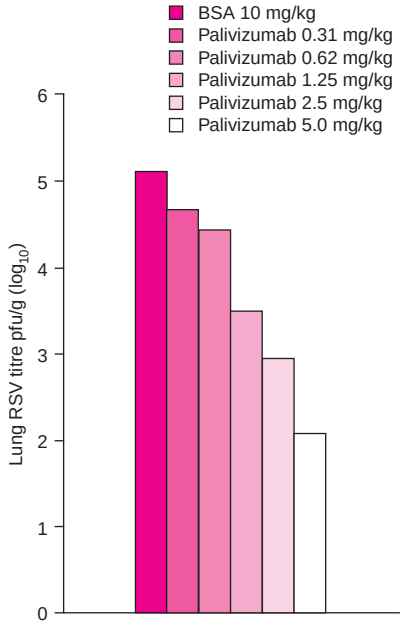


Fig. 1. Inhibition of RSV replication by palivizumab in lungs of cotton rats.[6] Cotton rats received intravenous BSA 10 mg/kg (n = 18) or palivizumab 0.31 (n = 7), 0.62 (n = 17), 1.25 (n = 18), 2.5 (n = 17) or 5 mg/kg (n = 15) 24 hours before challenge with 10^5 pfu of RSV. Lung RSV titre was determined 4 days after challenge. **BSA** = bovine serum albumin; **pfu** = plaque forming unit; **RSV** = respiratory syncytial virus.

• In a comparative study, 2 to 4-fold higher doses of felvizumab compared with palivizumab were required to provide similar levels of protection against RSV subtypes A and B in a cotton rat model of RSV infection.[9]

• There was no enhancement of RSV replication or enhanced pulmonary pathology after primary or secondary RSV challenge in cotton rats treated with subinhibitory doses of palivizumab.[6]

• Previous prophylaxis with palivizumab did not interfere with the development of a protective immune response after a subsequent challenge with RSV.[6]

• Palivizumab significantly decreased the neurogenic-mediated inflammatory response to RSV infections in a reactive airway disease model in rats.[10] Pretreatment with intraperitoneal palivizumab 15 mg/kg (n = 5) 5 days prior to capsaicin-stimulation of airway mucosae nerves in RSV-infected rats reduced Evans blue dye extravasation in response to RSV infection by 61% compared to placebo (118.3 *vs* 45.6 ng/ml; p = 0.0005). RSV-IGIV also significantly reduced neurogenic-mediated inflammation by 36% compared with placebo (93.2 *vs* 59.6 ng/ml; p = 0.0006).

Human Studies

• Palivizumab significantly decreased RSV replication in deep tracheal secretions of infants with RSV infection who were being mechanically ventilated in a multicentre, double-blind, randomised trial.[8] During the first 24 hours, the mean titre of RSV in deep tracheal secretions declined by 1.7 $\log_{10}$ plaque forming units (pfu)/ml in infants receiving intravenous palivizumab 15 mg/kg (n = 16) compared with a decline of 0.6 $\log_{10}$ pfu/ml in those receiving placebo (n = 17; p = 0.004). After 48 hours, the mean titre declined by 2.5 $\log_{10}$ versus 1.0 $\log_{10}$ pfu/ml, respectively (p = 0.012). There were no significant differences at 24 or 48 hours between treatment groups in any other parameter tested (white cell count, percentage neutrophils and myeloperoxidase or eosinophilic cationic protein concentration) in nasal and tracheal secretions.

2. Pharmacokinetic Profile

The pharmacokinetic properties of palivizumab have been investigated in infants ≤6 months of age born prematurely (≤35 weeks of gestation), infants with BPD who were ≤24 months of age[11-13] and in patients (ages not specified) who had undergone haematopoietic stem cell transplantation.[14]

High-Risk Infants

- Mean 30-day trough serum concentrations (C_{min}) of palivizumab in infants were consistently about 70 mg/L after repeat monthly doses of intravenous (n = 22)[13] or intramuscular (n = 48;[11] and n = 1002[12]) palivizumab 15 mg/kg (fig. 2). C_{min} exceeded 40 mg/L (concentration required to reduce pulmonary RSV replication by >99% in animals; see section 1) in 86% of infants after the second dose of intravenous palivizumab 15 mg/kg compared with 38% of those receiving 10 mg/kg,[13] and 0% of those receiving 3 mg/kg (intravenous)[13] or 5 mg/kg (intramuscular) doses.[11]

- The area under the plasma concentration-time curve from zero to infinity (AUC0-∞) after the first dose of intravenous palivizumab 15 mg/kg was 5295 (unit not specified); a comparable value was observed after the second dose.[13]

- Transient, nonspecific anti-palivizumab binding was observed in 1.2% of infants receiving palivizumab 15 mg/kg compared with 2.8% in the placebo group.[12]

- Palivizumab had a mean plasma elimination half-life ($t_{1/2}$) of 20 (range 19.3 to 26.8) days after intravenous administration[13] and approximately 24 days after intramuscular administration;[11] which is similar to that of human IgG_1.

Immunocompromised Patients

- Serum concentrations of palivizumab exceeded 40 mg/L, 21 days after intravenous palivizumab 15 mg/kg, in 77% of a total of 17 patients who had undergone haematopoietic stem cell transplant.[14]

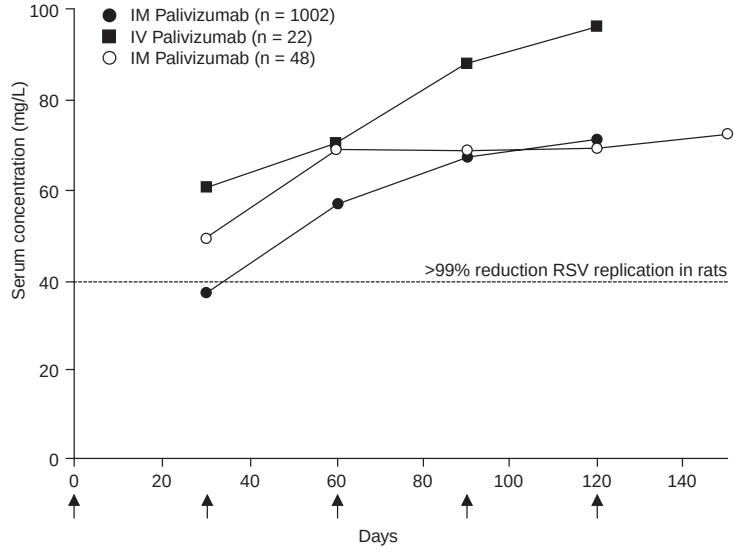


Fig. 2. Mean trough serum concentrations of palivizumab in infants at high risk of RSV infection. Infants received palivizumab 15 mg/kg intramuscularly (n = 1002[12] and n = 48)[11] or intravenously (n = 22)[13] every 30 days for up to 5 months. Arrows indicate the timing of each dose. Infants recruited were those born prematurely (≤35 weeks of gestation) who were ≤6 months of age or those with bronchopulmonary dysplasia who required recent or ongoing treatment and were ≤2 years of age. The concentration of palivizumab required to reduce RSV replication by >99% in cotton rats is indicated on the graph. **RSV** = respiratory syncytial virus.

• In the same group of patients, mean $t_{1/2}$ was 22.4 (range 9.9 to 56.7) days in those with no RSV infection (n = 6). Mean $t_{1/2}$ was shortened (10.7 days; range 4.5 to 22.2 days) in patients (n = 15) with active RSV infection who were receiving concomitant ribavirin.[14]

3. Therapeutic Trials

The efficacy of prophylactic palivizumab has been investigated in a single, large, multicentre, double-blind, randomised trial (IMpact-RSV) in which high-risk infants received an intramuscular injection of palivizumab 15 mg/kg (n = 1002) or placebo (n = 500) every 30 days for 5 months during the high risk seasons of winter and spring.[12] Infants recruited were those born prematurely (≤35 weeks of gestation) who were ≤6 months of age or those with BPD who required recent (within 6 months) or ongoing treatment and were ≤2 years of age. The primary end-point was the incidence of hospitalisation attributable to confirmed RSV infection; secondary end-points included the total number of days in hospital, days with increased supplemental oxygen requirement, days with a moderate to severe lower respiratory tract infection, admissions to and duration of intensive care, and the incidence and duration of ventilation.

• Palivizumab significantly reduced the incidence of hospitalisation attributable to confirmed RSV infection in at-risk infants by 55% compared with placebo;[12] the rate of hospitalisation attributable to RSV infections was 4.8% in infants receiving palivizumab 15 mg/kg compared with 10.6% in the placebo group (p = 0.00004).

• The incidence of RSV-attributable hospitalisation was effectively reduced in infants receiving palivizumab irrespective of the presence of individual risk factors such as BPD, low gestational age at birth and bodyweight (fig. 3).[12]

• In addition, palivizumab showed clinical efficacy according to secondary end-points.[12] Infants receiving palivizumab had significantly fewer total days of hospitalisation with confirmed RSV infection (36.4 *vs* 62.6 days per 100 infants with placebo; p < 0.001); fewer days with increased supplemental oxygen (30.3 vs 50.6 days per 100 infants with placebo; p < 0.001); and fewer days with moderate to severe lower respiratory tract illness/infection (29.6 *vs* 47.4 days per 100 infants with placebo; p < 0.001). Palivizumab recipients were also admitted less frequently to intensive care (1.3 *vs* 3% per 100 infants with placebo; p = 0.026), but had a slightly longer duration in intensive care (13.3 *vs* 12.7 days per 100 infants with placebo; p = 0.023).

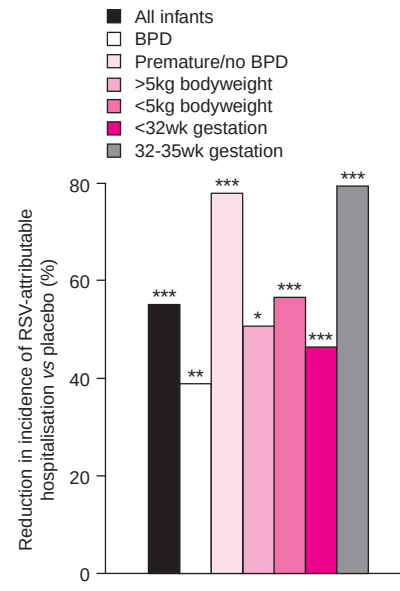


Fig. 3. Effects of prophylactic palivizumab on the incidence of RSV-attributable hospitalisation in different subgroups of high-risk infants. In a multicentre, double-blind, randomised trial, infants received intramuscular palivizumab 15 mg/kg (n = 1002) or placebo (n = 500) every 30 days for 5 months during the winter and spring.[12] Infants included those born prematurely (≤35 weeks of gestation) ≤6 months of age and those with BPD who required ongoing treatment and were ≤2 years of age. **BPD** = bronchopulmonary dysplasia; **RSV**= respiratory syncytial virus; * p = 0.014; ** p = 0.038; *** p < 0.001 *vs* placebo.

• There were no significant differences between treatment groups in the incidence or total number of days of ventilation, the incidence of hospitalisation or total number of days attributable to causes other than RSV infection, or the proportion of children with at least one episode of otitis media.[12]

4. Tolerability

High-Risk Infants

• Intramuscular palivizumab was well tolerated in 1002 infants at high risk of RSV infection (IMpact-RSV study).[11,12] The incidence of adverse events judged to be related to treatment was similar in both placebo (10%) and palivizumab (11%) groups;[12] there were no significant differences between the 2 treatment groups in incidence of the most common events (fig. 4). The most common adverse events were fever, irritability and injection site reaction. Discontinuation of palivizumab as a result of adverse events was rare (0.3%).

• Intravenous palivizumab was also well tolerated in 62 infants at high risk of RSV infection in a dose-finding study.[13] Adverse events were reported in 15% of infants in the placebo group and 10, 0 and 23% of infants receiving palivizumab 3, 10 and 15 mg/kg, respectively; most frequently reported adverse events after intravenous administration were fever (n = 3), right upper lobe pneumonia (n = 2) and infusion site infiltration (n = 2).

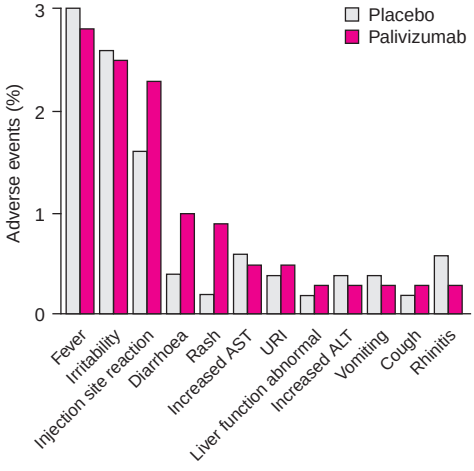


Fig. 4. Most frequently reported adverse events judged to be potentially related to palivizumab in infants at high risk of RSV infection. In a multicentre, double-blind, randomised trial, infants received an intramuscular injection of palivizumab 15 mg/kg (n = 1002) or placebo (n = 500) every 30 days for 5 months during the high-risk season.[12] **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **RSV** = respiratory syncytial virus; **URI** = upper respiratory tract infection.

• Reactions at the site of intramuscular palivizumab injection were uncommon (2.7 *vs* 1.8% in the placebo group) and were of short duration.[12] These reactions primarily involved erythema, pain, induration/swelling and bruising.

• A second 5-dose course of palivizumab 15 mg/kg was well tolerated in 56 high-risk infants who had received palivizumab in the previous RSV season.[15] No local or systemic reactions suggesting an immune-mediated response were reported.

• Palivizumab has no reactivity against measles-mumps-rubella or varicella vaccines, and can be administered concurrently with these vaccines.[16]

5. Palivizumab: Current Status

Palivizumab is a humanised monoclonal antibody which inhibits pulmonary RSV replication and fusion. It is currently marketed in North and South America, Kuwait and Australia, and received a positive opinion for approval by the Committee for Proprietary Medicinal Products (CPMP) and is scheduled to be introduced in Europe in late 1999 for prophylactic use in infants at high risk of RSV infection. It effectively reduced the incidence of RSV-attributable hospitalisation and was well tolerated in high-risk infants in a large, multicentre clinical trial. Ongoing studies will more clearly define its place in the prevention of RSV infections.

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