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Original Article

Effectiveness and Safety of Palivizumab for the Prevention of Serious Lower Respiratory Tract Infection Caused by Respiratory Syncytial Virus: A Systematic Review

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Abstract

Objective Palivizumab is a humanized monoclonal antibody approved for the prevention of serious lower respiratory tract infection (LRTI) caused by respiratory syncytial virus (RSV) in infants and young children at high risk of RSV disease. This systematic review summarized evidence on the effectiveness and safety of palivizumab when used in approved populations.

Study Design A systematic review of Phase III trials and observational studies was conducted according to the population, intervention, comparator, outcome, timing, setting (PICOTS) approach (PROSPERO, CRD42021281380). Target populations consisted of infants with a history of premature birth (≤35-week gestational age) and children aged <2 years with bronchopulmonary dysplasia (BPD) or with hemodynamically significant congenital heart disease (hs-CHD). Outcomes of interest included RSV-related hospitalization, admission to intensive care unit (ICU), requirement for mechanical ventilation, treatment-related adverse events (AEs), and RSV-related deaths. Information sources were literature search (Ovid MEDLINE and Embase), pragmatic searches, and snowballing (covering the period up to 07 September 2021).

Results A total of 60 sources were included (5 Phase III trials and 55 observational studies). RSV-related hospitalization rates following palivizumab prophylaxis in Phase III trials were 1.8% in premature infants and 7.9% in children with BPD, which were significantly lower than rates in placebo arms. In the real-world setting, similar hospitalization rates were found (0.7–4.0% in premature infants [16 studies] and 0–5.5% in patients with BPD [10 studies]) with ICU admission reported in 0 to 33.3% of patients hospitalized for RSV. In Phase III trials, RSV-related mortality rates were 0.2 and 0.3%, while AEs occurred in 11% of premature and/or BPD patients and 7.2% of hs-CHD

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patients, consisting mainly of injection site reaction, fever, and diarrhea. Similar results were found in observational studies.

Conclusion This systematic review supports the effectiveness and safety of palivizumab in the indicated populations.

Key Points

- Systematic review supports the positive benefit-risk profile of palivizumab in the indicated populations.
- Real-world safety and effectiveness of palivizumab are consistent with Phase III trials results.
- Palivizumab reduces RSV-related hospitalizations, ICU admissions, and need for mechanical ventilation.

Respiratory syncytial virus (RSV) is a major cause of death globally in children below 5 years of age.[1] The clinical manifestations of RSV vary widely from an asymptomatic form to a mild, self-limiting upper respiratory tract infection, and to severe lower respiratory tract infection (LRTI), which may lead to hospitalization and death.[2–4] It is estimated that nearly 33.8 million new cases of RSV-associated LRTI occur worldwide every year in children less than 5 years old, leading to 3.4 million hospital admissions.

Palivizumab (SYNAGIS) is a humanized monoclonal antibody that was approved by the U.S. Food and Drug Administration (FDA) in 1998 for the prevention of serious LRTI caused by RSV in infants and young children at high risk of RSV disease. As per FDA approval, the indicated populations are the following: (1) patients with a history of premature birth ($\leq$35-week gestational age [WGA]) and $\leq$ 6 months of age at the beginning of RSV season; (2) patients with bronchopulmonary dysplasia (BPD) who required medical treatment within the previous 6 months and $\leq$24 months of age at the beginning of RSV season; and (3) patients with hemodynamically significant congenital heart disease (CHD) and $\leq$24 months of age at the beginning of RSV season.[5] However, recommendations for RSV immunoprophylaxis have evolved over time and current clinical practice may not necessarily reflect original indications.[6,7]

Despite these changes, the effectiveness and safety of palivizumab have been investigated in several studies, including a review of interventional and noninterventional studies (i.e., randomized controlled trials [RCTs], open-label non-comparative clinical trials, and prospective observational studies/registries) published in 2014, which showed heterogeneity of study populations and methods between studies.[8] The current systematic review aimed at summarizing and updating all available evidence on the efficacy, effectiveness, and safety of palivizumab from both the interventional and real-world clinical practice settings.

Materials and Methods

The systematic review, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, included Phase III trials and observational studies on palivizumab for the prevention of serious LRTI caused by RSV, published up to 07 September 2021 (PROSPERO, CRD42021281380). The review followed the PICOTS (population, intervention or exposure, comparator, outcomes, time period, setting) approach. Target populations consisted of the above-listed three indicated populations, and outcomes of interest were RSV-related hospitalization, RSV-related admission to intensive care unit (ICU), requirement for mechanical ventilation, long-term morbidity of RSV, treatment-related adverse events (AEs), and RSV-related death. No geographical restriction was applied.

Literature search was conducted in Ovid MEDLINE and Embase using free-text keywords and thesaurus terms (search strategies available in ►**Supplementary Table S1**, available in the online version). Duplicate sources (i.e., same study and same citation) were eliminated using automated procedures. For additional sources, pragmatic searches of web sources, including websites of relevant learned or clinical societies and related conference proceedings, were conducted, along with a hand search of the reference list of retained studies (snowballing).

Study selection and data extraction were conducted independently by two assessors (with conflicts resolved by a third assessor). Eligibility criteria for the selection of relevant sources were based on the PICOTS and are listed in ►**Table 1**. At stage 1, literature search outputs were screened based on titles and abstracts and percent agreement between assessors was determined. A review of full-text articles was conducted at stage 2 to confirm the eligibility of sources retained after screening. Reasons for the exclusion of sources at this stage were documented.

The methodological quality of retained full-text publications was assessed using the Cochrane Collaboration's tool for assessing the risk of bias (risk of bias in nonrandomized studies [ROBINS-I])[9] for nonrandomized studies of interventions, the revised Cochrane risk-of-bias tool for randomized trials (RoB-2)[10] for RCTs, and the Joanna Briggs Institute (JBI) critical appraisal tools for observational studies.[11] To minimize the risk of bias, only studies deemed of moderate or good methodological quality were retained for the qualitative summary of findings. There was no attempt to contact study authors for supplementary data.

Results

The flow of search results through the different stages of the selection process is presented in the PRISMA flow chart

Table 1 Eligibility criteria for the selection of sources included in the systematic review on effectiveness and safety of palivizumab

Inclusion criteria	Exclusion criteria
• Studies conducted in humans • Studies that included, either as the study population or as a subgroup analysis, infants and children who received palivizumab (SYNAGIS) according to approved indications • Studies that reported on the safety, efficacy, and/or effectiveness of palivizumab • Full-text articles, conference proceedings including abstracts and posters, or reports • Original research articles, reviews, and meta-analyses (the latter two were used for snowballing only) • For studies with multiple publications, only the latest publication on each outcome of interest was retained	• Off-label populations • Case reports • Letters to the editors and editorials • Opinions • Phase I and II clinical trials • Nonclinical and experimental studies • Studies reporting preliminary results (later published as full text)

(►**Fig. 1**). The literature search yielded 2,250 sources of which 461 duplicates were removed. After stage 1 screening, 254 publications were retained (the agreement rate between assessors was 87.9%). At stage 2, 197 sources were further excluded, mainly because they did not report on outcomes of interest ($n = 63$; 32.0%). Pragmatic searches and snowballing yielded 3 additional relevant sources. A total of 60 sources (5 Phase III trials and 55 observational studies) fulfilled the eligibility criteria and were thus included in the review. The characteristics, key findings, and methodological quality assessment (only for full-text publications) of retained studies are described in ►**Supplementary Tables S2** (available in the online version; clinical trials)[12–16] and ►**Supplementary Tables S3** (available in the online version; observational studies).[17–71]

Methodological Quality of Retained Studies

All clinical trials identified in this review were deemed to have a low risk of bias as measured with the RoB-2 and ROBINs-I tools. The methodological quality of observational studies published as full-text articles was assessed using the JBI critical appraisal tools for cohort studies ($n = 28$), case series (i.e., noncomparative cohort studies; $n = 9$), cross-sectional studies ($n = 3$), and case-control studies ($n = 1$). Based on this evaluation, 23 (56.1%) of the 41 observational studies assessed were deemed of good methodological

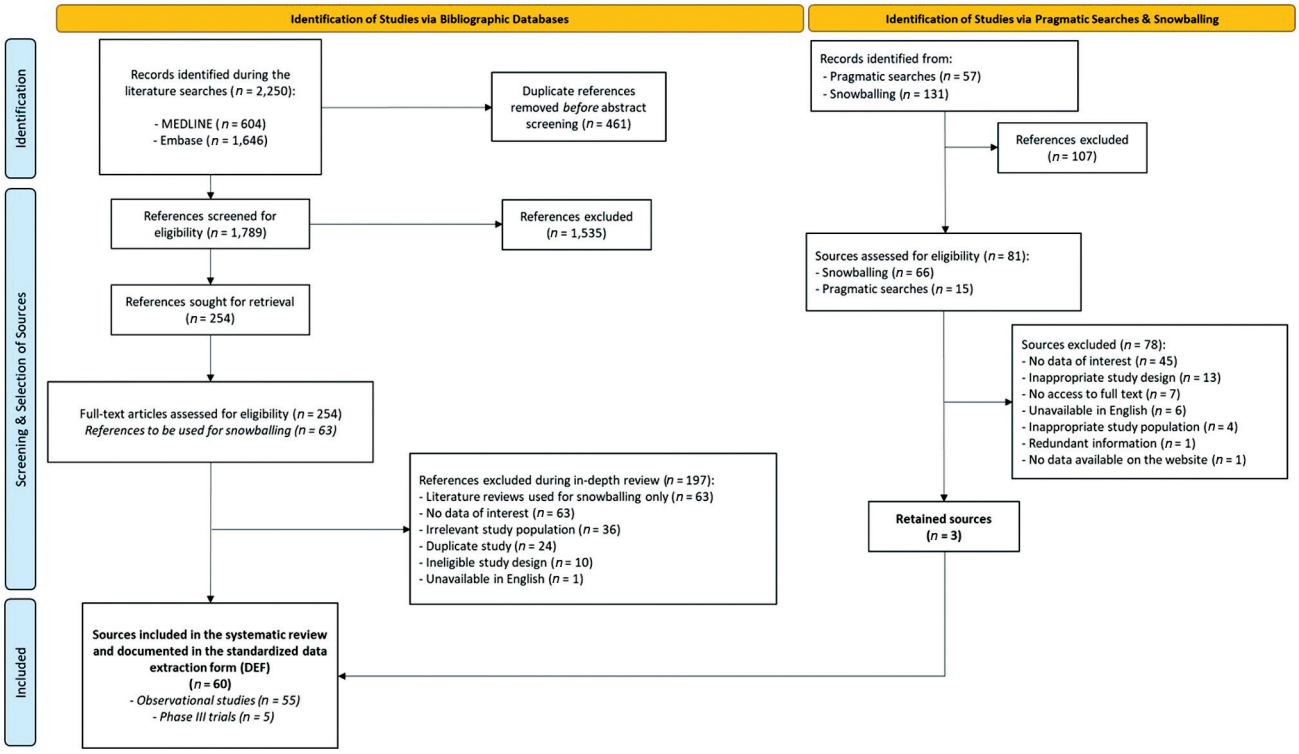

Fig. 1 PRISMA flow chart of searches on safety and effectiveness of palivizumab. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

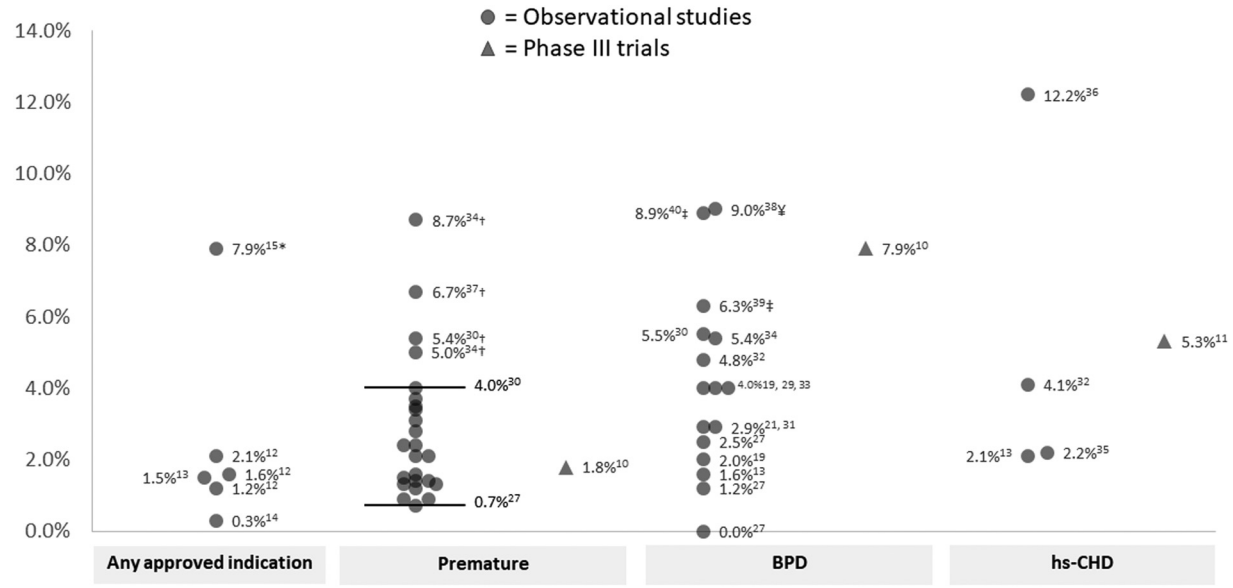

Fig. 2 Rates of RSV-related hospitalizations among palivizumab-treated patients in observational studies and phase III trials. *Reported over a 7-month follow-up period in the United States. †Higher rates observed in extremely premature infants (≤28 WGA). ‡Higher rates observed in BPD patients with a history of premature birth and low birth weight. ¥Higher rate observed in patients with severe BPD. BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; RSV, respiratory syncytial virus; WGA, week gestational age.

quality, and the remaining were considered to be of moderate methodological quality. Therefore, no studies were excluded from the narrative summary of findings due to the high risk of bias.

Rates of Respiratory Syncytial Virus-Related Hospitalization

According to two Phase III trials, RSV-related hospitalization rates were significantly lower in patients who received palivizumab prophylaxis compared with a placebo, for each of the indicated populations. Reported rates in the treated and placebo arms were, respectively, 1.8 and 8.1% in premature infants ($p < 0.001$),[12] 7.9 and 12.8% in patients with BPD ($p < 0.001$),[12] and 5.3 and 9.7% in patients with hs-CHD ($p = 0.003$).[14] In the IMpact trial which included both premature infants and patients with BPD, the hospital length of stay was significantly lower in patients who received palivizumab compared with placebo (36.4 and 62.6 days per 100 children, respectively, $p < 0.001$).[12] Similar results were reported in patients with hs-CHD, with a total number of days of hospitalization of 57.4 and 129.0 per 100 children, respectively, in the treated and placebo arms, corresponding to a statistically significant reduction of 56% associated with the use of palivizumab ($p = 0.003$).[14]

In the real-world setting, 28 studies reported rates of RSV-related hospitalization among patients who received palivizumab prophylaxis according to approved indications. Among these, four included patients who received palivizumab for any of the FDA-approved indications and reported estimates ranging from 0.3 to 2.1% with a higher estimate of 7.9% observed over a 7-month follow-up period in the United States.[17,43,58,66] Considering each indicated population individually, observed rates ranged between 0.7 and 4.0% in premature infants (16 studies),[18,26,27,37,41,42,47,49,51,52,57,61,64,66,69,71] between 0 and 5.5% in patients with BPD (10 studies),[18,33,37,47,50,55,56,66,69,71] and between 2.1 and 12.2% in patients with hs-CHD (4 studies),[28,33,66,68] as presented in ►Fig. 2. Higher rates were found in extremely premature infants (5.0,[56] 5.4,[71] and 6.7%[24] in children born ≤28 WGA, and 8.7% in those born <27 WGA[56]), in patients with severe BPD (9.0%),[31] as well as in BPD patients with a history of premature birth and low birth weight (6.3 and 8.9%).[30,54] According to nine observational studies, palivizumab prophylaxis in premature infants and in BPD patients is associated with a significant decrease in RSV-related hospitalization compared with untreated patients[18,24,52,54–56,61,69,71] In a retrospective cohort study of 789 infants born at 29 through 32 WGA (262 received palivizumab and 527 did not), conducted in Austria over the period from 2004 to 2012, a risk reduction of 50% in RSV-related hospitalizations associated with the use of palivizumab was observed (odds ratio: 0.504 [95% confidence interval [CI], 0.259–0.981]).[61] In this study, patients receiving palivizumab may have concomitant BPD or CHD as the selection of patients for RSV prophylaxis was based on a risk score tool that considered these underlying diseases as the main risk factors for RSV, therefore requiring palivizumab. Similarly, in Spain, the IRIS study group reported that premature infants (≤32 WGA) with or without BPD who do not receive palivizumab had a higher risk of RSV-related hospitalization compared with those who received prophylaxis (odds ratio: 3.86 [95% CI, 2.83–5.25]).[71]

In a single-center retrospective cohort study conducted in Singapore on 407 infants born <32 WGA ($n = 109$ palivizumab users and $n = 306$ untreated patients), the incidence rate of RSV-related hospitalizations within 6 months post-initial discharge from the neonatal service was significantly lower in treated than in untreated patients (18.3 vs. 143.9 per 1,000 patient-years, $p = 0.01$).[52] However, incidence rates did

not differ significantly at 7 to 9 months (0 vs. 92.7 per 1,000 patient-years, $p = 0.25$) and at 10 to 12 months (81.6 vs. 41.8 per patient-years, $p = 0.75$).

In the hs-CHD population, a retrospective cohort study reported an incidence rate of 27.7 per 1,000 patient-years (95% CI, 17.5–44.2) in infants who received palivizumab prophylaxis ($n = 705$) compared with 52.9 per 1,000 patient-years (95% CI, 38.0–74.1) in those who did not ($n = 705$) ($p < 0.05$).[48]

Rates of Intensive Care Unit Admission and Intensive Care Unit Length of Stay

In a Phase III trial conducted in hs-CHD infants, there was no significant difference in the rate of ICU admission among patients hospitalized for RSV infection between the palivizumab and placebo arms (38.2 vs. 38.1%).[14] In this trial, the ICU length of stay related to RSV infection was 15.9 days per 100 children who received palivizumab ($n = 639$) compared with 71.2 days per 100 children who did not receive palivizumab ($n = 648$), corresponding to a reduction of 78% associated with the use of palivizumab ($p = 0.08$). In the IMpact trial which included both premature infants and patients with BPD, the rate of ICU admission among children hospitalized for RSV was significantly lower in patients who received palivizumab compared with placebo (1.3 and 3.0%, respectively, $p = 0.026$). In this study, the ICU length of stay in the palivizumab and placebo arms were, respectively, 13.3 and 12.7 days per 100 children ($p = 0.023$).[12]

In the real-world setting, rates of ICU admission in premature infants who received prophylaxis with palivizumab and who were hospitalized for an RSV infection were reported in nine studies.[26,27,33,41,52,57,61,64,69] Of these, most (66.7%; $n = 6$) reported rates ranging from 16.6% to 33.3%.[26,27,33,41,61,64] A lower rate of 8.3% was found in a claims-based retrospective cohort study from Taiwan that included extremely premature infants (≤ 28 WGA).[69] Also, in a retrospective cohort study from Canada that included 87 palivizumab-treated infants born 29 to 32 WGA, only three patients were hospitalized due to RSV, of which two were admitted to the ICU (66.7%).[57] Finally, in a single center retrospective cohort study from Singapore, none of the three infants born <32 WGA who were hospitalized for RSV infection following prophylaxis with palivizumab required ICU admission.[27] In this study, 15.6% of the 32 infants who did not receive palivizumab and were hospitalized for RSV were admitted to the ICU. Similar to the population of premature infants, ICU admission rates of 23.7,[33] 24.6,[68] and 33.3%[28] were found in infants with hs-CHD who received palivizumab prophylaxis and were hospitalized for an RSV infection. In infants with BPD, heterogeneous estimates were found in five studies due to differences in study populations and countries,[33,50,54,55,69] each described below.

The first was an administrative claims-based study conducted in Taiwan, in which no ICU admission was observed in patients who received palivizumab.[69] According to a multinational prospective cohort study based on the CARESS and Torino-Verona Northern Italy Network registries, 7.0% of the 57 infants with BPD hospitalized with RSV during the RSV season required care in the ICU following prophylaxis with palivizumab.[33] Also, based on the CARESS registry between 2005 and 2015, 22.3% of BPD patients treated with palivizumab during their first year of life and hospitalized for RSV were admitted to the ICU.[50] Two studies reported a higher estimate of ICU admission (33.3% each) in patients with BPD who were hospitalized for RSV. The former consisted of a retrospective cohort study conducted over the period from 2004 to 2009 in South Korea,[55] while the latter included BPD infants who were also premature and had a very low birth weight.[54]

Rates and Duration of Mechanical Ventilation/Intubation

In a Phase III trial that included young children with hs-CHD, no statistically significant differences in the proportion of patients hospitalized for an RSV infection who required mechanical ventilation were found between the palivizumab and placebo arms (23.5 and 22.2%, respectively).[14] In this trial, the use of palivizumab decreased the duration of mechanical ventilation by 88% compared with placebo (6.5 vs. 54.7 days per 100 children, respectively, $p = 0.224$). In the IMpact trial which included both premature infants and patients with BPD, the duration of use of mechanical ventilation among children hospitalized for RSV in the palivizumab and placebo groups was, respectively, 8.4 and 1.7 days per 100 children ($p = 0.224$).[12]

According to six observational studies, the need for mechanical ventilation or intubation in premature infants hospitalized with RSV following palivizumab prophylaxis ranged between 5.6 and 14%[27,33,41,61,64,69] and no significant difference was observed between palivizumab users and nonusers.[61,69] A higher rate of 33.3% was reported in two studies including children born at 29 to 32 WGA.[26,57] In infants with BPD, reported rates varied across five studies, ranging from 0% in BPD patients born at 29 to 35 WGA in Taiwan[69] to 7.0% in BPD patients in Canada or Italy,[33] and even as high as 25% in BPD patients born at $\leq$35 WGA with low birth weight ($\leq$1,500 g),[30] or 33.3% in patients with BPD born prematurely with very low birth weight.[54] Among patients with hs-CHD (three studies), the rates were 8.8,[68] 22.0,[33] and 25.9%.[28]

Oxygen Requirement among Respiratory Syncytial Virus

Hospitalized Patients

According to two Phase III trials, palivizumab prophylaxis was associated with a statistically significant reduction in the duration of supplemental oxygen requirement in patients hospitalized with RSV infection.[12,14] In young children with hs-CHD, total days of oxygen requirement in the palivizumab and placebo groups were, respectively, 27.9 and 101.5 days per 100 children ($p = 0.014$).[14] Similarly, in a combined population of premature infants and patients with BPD (IMpact trial), the duration of supplemental oxygen requirement in patients hospitalized for RSV was 30.3 and 50.6 days per 100 children, respectively, in those who received palivizumab and placebo ($p < 0.001$).[12]

In the real-world setting, based on four studies, the proportion of premature infants hospitalized for an RSV infection who required supplemental oxygen following palivizumab prophylaxis were heterogenous, ranging from 14 to 33.3%.[26,27,41,61] In patients with BPD and hs-CHD, reported rates of oxygen therapy requirement among those who were hospitalized for an RSV infection following palivizumab prophylaxis were 25.0 and 14.0%, respectively.[30,68]

Long-Term Morbidity in Patients who Received Palivizumab Prophylaxis

Based on five observational studies conducted in premature infants, wheezing was the most commonly investigated long-term morbidity in those treated with palivizumab.[24,29,38,40,51] Rates of physician-diagnosed recurrent wheezing in the palivizumab group ranged from 6.4 to 12.8%.[29,38,40] Another study reported a higher estimate of 56.3% after 11 years of follow-up.[51] However, no details on the method for case identification and/or diagnostic ascertainment were reported. There was a significant risk reduction of physician-diagnosed recurrent wheezing associated with the use of palivizumab compared with untreated patients (risk ratio [RR], 0.34, 95% CI, 0.19–0.60[29]; RR, 0.49, 95% CI, 0.27–0.88[40]). When considering caregiver-reported recurrent wheezing, similar results were found. More specifically, comparing patients treated with palivizumab to untreated infants, a multicenter prospective cohort study conducted in Canada, Germany, The Netherlands, Poland, Spain, and Sweden reported an RR of 0.51 (95% CI, 0.33–0.78).[40] In extremely premature infants (<29 WGA), the rate of parent-reported recurrent wheezing following RSV infection in the palivizumab group was significantly lower than that in untreated patients during the first 2 years of life (26.7 vs. 69.7%, $p = 0.008$),[24] but no statistically significant difference was observed at age 7 to 10 years (13.3 vs. 18.2%).[24] One study evaluated the occurrence of atopic asthma following RSV infection and found no statistically significant effect of palivizumab (OR, 1.27, 95% CI, 0.60–2.70).[38] In a study conducted in children aged 7 to 10 years, lower rates of upper respiratory tract infection were observed in patients who received prophylaxis with palivizumab as infants versus nonusers (30.0 vs. 69.7%, $p < 0.05$).[24] No statistically significant difference in lung function parameters was observed among adolescents (13–18 years old) born <29 WGA who received palivizumab as prophylaxis or not.[34]

Treatment-Related Adverse Events

The frequency of AEs associated with the use of palivizumab was low in both the clinical trial (0–12% of patients) and real-world settings (0–7% of patients). In clinical trials, no serious AEs (SAEs) attributable to palivizumab were reported and rates of AEs were not statistically different between patients who received palivizumab or placebo for all indications: 11 versus 10% in patients with a history of premature birth (<35 WGA) and/or BPD,[12] and 7.2 versus 6.9% in patients with hs-CHD.[14] Overall, the most common AEs were fever, injection site reaction, diarrhea, and rash.

In the real-world setting, rates of AEs associated with palivizumab were 2.1,[26] 4.0,[55] 6.4,[18] and 7%[46] and the rates of SAEs were 0.3[18] and 1.4%.[26] The most common events were local erythema, systemic fever, local pain, irritability, vomiting, and diarrhea.[18,26,55] Based on one study, serious events, defined as any AE resulting in death, life-threatening situation, inpatient hospitalizations, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other medically important events, that were possibly related to palivizumab were reported in two patients and included infection and bronchiolitis reported in one patient and pneumonia and conjunctivitis reported in the other patient.[26] In a retrospective cohort study of 2,018 children aged ≤2 years with hs-CHD, there was no increased risk of serious infection or serious arrhythmia associated with the use of palivizumab compared with unmatched controls (OR of 0.95 and 1.64, respectively, for each SAE).[67]

Respiratory Syncytial Virus-Related Mortality in Patients who Received Palivizumab Prophylaxis

In two Phase III trials, RSV-related mortality in the palivizumab arm was as low as 0.2% in premature infants[12] and 0.3% in infants with hs-CHD.[14] In both trials, no significant differences were observed between palivizumab and placebo recipients.

In the real-world setting, 10 observational studies including a nonselected population of infants treated with palivizumab for either of the three approved indications reported no deaths attributable to RSV.[18,25,26,31,36,43,55–57,70] In two studies restricted to BPD or hs-CHD patients, RSV-related deaths occurred in 1.1% of children treated with palivizumab.[30,68]

Discussion

This systematic review included 5 Phase III clinical trials and 55 observational studies on palivizumab as prophylaxis for RSV infection in children at high risk for severe RSV disease. Across studies, efficacy, effectiveness, and safety of palivizumab assessed using outcomes of RSV-related hospitalization (rates and length of stay), ICU admission (rates and length of stay), need for mechanical ventilation, treatment-related AEs, and RSV-related mortality were well documented in both the interventional and noninterventional settings. In contrast, the effect of palivizumab on the need for supplemental oxygen and on the long-term morbidity associated with RSV infection was scarcely documented.

In the clinical trial setting, rates of RSV-related hospitalization following prophylaxis with palivizumab varied according to indication, with lower rates observed in premature infants than in the BPD or hs-CHD population and were significantly lower compared with placebo. Similarly, in observational studies for all approved indications, the use of palivizumab was found to significantly reduce RSV-related hospitalizations compared with untreated patients. For all subpopulations of interest, RSV-related hospitalization rates in patients treated with palivizumab were similar to those reported in the 2014 systematic review.[8] These findings

support the effectiveness of palivizumab in preventing RSV infection and associated complications in patients at high risk for severe RSV disease and are consistent with findings from the 2014 systematic review.[8] However, assessment of the feasibility of conducting a meta-analysis highlighted important clinical and methodological heterogeneity across studies, therefore pooling data from retained studies would not be recommended according to Cochrane guidelines.[72]

Palivizumab was also found to significantly reduce ICU admission and ICU length of stay. However, its impact on the reduction of the duration of mechanical ventilation compared with placebo was not statistically significant.[12,14]

In the previous review conducted by Wegzyn et al in 2014, evidence suggested that palivizumab is associated with reduced infant mortality but that more research was needed to confirm the results.[8] The current review, therefore, adds to the data presented in 2014 by summarizing the available data on RSV-related mortality rates in infants treated with palivizumab as well as long-term morbidity following palivizumab prophylaxis. RSV-related mortality rates were low and did not vary across settings (i.e., clinical trials and observational studies) or across indicated populations. Long-term morbidity following palivizumab prophylaxis was only documented in observational studies conducted in patients with a history of premature birth. In most studies, the use of palivizumab was associated with a significant decrease in recurrent wheezing.

The frequency of AEs, including SAEs, associated with the use of palivizumab was low in both the clinical trials and real-world settings, and results were similar across all indicated populations. Injection site reaction, fever, and diarrhea were the most frequent AEs observed in clinical trials, whereas fever, rhinitis, and pain at the injection site were the most frequent in observational studies.

Limitations and Strengths

A limitation of this review is that included studies were mainly those that led to publications in the scientific literature and indexed in bibliographical databases such as MEDLINE or Embase using predefined MeSH and Emtree terms and keywords included in the search strategy. To mitigate publication bias and to enhance the scope of the search, pragmatic searches as well as snowballing were conducted. Another limitation consisted of the absence of information in nearly half of the publications on the criteria used to ascertain RSV cases, which limits the interpretation of findings regarding RSV-related hospitalizations, ICU admissions, and need for mechanical ventilation.

The strengths of the review were the following. The methodological quality of studies was evaluated using validated assessment tools based on expert critical review. Based on this assessment, all studies retained in this review were considered to be of moderate or good methodological quality with a low risk of bias. The screening and data extraction processes were performed independently by two reviewers with discrepancies resolved by a third independent assessor. A major strength of this review is that findings on the use of palivizumab published worldwide from over more than two decades (1998–2021) were summarized, yet results were overall consistent, therefore supporting its positive and consistent benefit-risk profile across all indicated populations in both the clinical trial and real-world practice settings.

Conclusion

The effectiveness of palivizumab for the prevention of RSV-related serious LRTI was well-documented in the literature, and findings from the real-world clinical practice setting are consistent with those reported in Phase III trials with regard to reduced RSV-related hospitalizations, ICU admission, and need for mechanical ventilation. The frequency of AEs associated with the use of palivizumab was low, and the safety profile was consistent with the safety information provided in the palivizumab product label. Results from this systematic review thus support the positive benefit-risk profile of palivizumab in the indicated populations.

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Conflict of Interest

A.B., T.C., C.G., and Y.M. are employees of YOLARX Consultants that received funding from Sobi for the conduct of this review. T.G., A.O., J.S., J.Y., and M.W. are employees of Sobi.

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