Immunizations

Palivizumab for the prevention of rsv infection in children with cystic fibrosis

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Background

Respiratory syncytial virus (RSV) is the leading cause of hospitalisation for children under 5 years of age and causes excess mortality in the elderly worldwide, resulting in considerable morbidity and mortality. RSV directly impairs the mucus clearance mechanisms in the lung. The resultant mucus stasis facilitates bacteria infection, progressive lung disease and consequently respiratory failure.

Morbidity and mortality from severe RSV infection is also increased by comorbidity as pre-existing diseases. Children with CF are more likely to require hospitalization and deterioration in lung function during a respiratory virus season, compared with children without CF. In a previous review paper (Elnazir B et al. 2012) data were in favor of a higher risk of hospitalization for severe or persistent respiratory disease in the first year of life in infants with CF and RSV. But further studies did not confirm these data.

In a retrospective cohort study (Winterstein AG. 2013), that examined a cohort of 1974 children 0 to 2 years of age with CF diagnosis utilizing Medicaid Extract files from 27 states of USA from 1999 to 2006 linked to the National Cystic Fibrosis Registry, it was demonstrated that hospitalizations for acute respiratory illness with possible RSV contribution was low, as well as no potentially positive effects of palivizumab (PVZ) on hospitalization incidence rates were detected.

In a large, Canadian prospective (2005-2017) observational multicenter study (Mitchell I et al. 2021) a total of 25,003 infants (56.3% male) at high risk for RSV infection as prematurity (63.3%), "miscellaneous" (17.8%) including CF, hemodynamically significant congenital heart disease (10.5%), bronchopulmonary dysplasia/chronic lung disease (8.4%) were enrolled at 32 sites.These babies performed 109,579 PVZ injections. Three hundred thirty-seven hospitalized children were RSV-positive (overall RSVH 1.6%). Risk factors for RSVH included having siblings, attending daycare, family history of atopy, smoking exposure, and crowded household. Infants with 5 risk factors were 9.0 times (95% CI or confidence interval 4.4-18.2; $p < 0.0005$) more likely to have RSVH than infants without risk factors. Three adverse events occurred; none was fatal. Use of PVZ increased steadily for children with miscellaneous conditions and medical complexity.

Prevention strategies for RSV include maternal immunization, immunization of infants with vaccines, immunization of infants with licensed mAbs (palivizumab), and immunization of infants with long-acting mAbs (e.g., nirsevimab, MK-1654). Palivizumab is a humanized monoclonal antibody directed against the RSV F glycoprotein as effective in reducing RSV hospitalization rates and is recommended for prophylaxis in high-risk children with other conditions (Homaira N et al. 2014). However, it is unclear whether Palivizumab can prevent RSV hospitalizations in children with CF. Palivizumab is restricted to a small population of infants and does not offer a solution for all-infant protection. Data from an audit performed at a tertiary hospital in Ireland including all children with CF, <24 months old, who received palivizumab over a five year period (n=19) compared to a retrospective control group of 30 patients, supported for prophylactic use of palivizumab in CF patients under 2 years (Linnane B. 2015).

There is still no approved vaccine available, although the disease can be curtailed by RSV-specific monoclonal antibody. The only antiviral drug approved for the treatment of RSV infection is ribavirin aerosol, but this treatment is cumbersome and its efficacy is questionable. In the past a new antiviral, GS-5806, which interferes with virus–cell fusion, was proved to be efficacious in experimental RSV infections in adults (De Clercq E et al. 2015).

Vaccine availability in infants could be considered in several conditions, including the immaturity of the infant immune system, highlighting that future pediatric vaccines will most likely be used in older infants (>6 months of age) and children (Esposito S et al. 2022).

Issues

1. To determine the efficacy of Palivizumab compared to placebo in children with CF.
2. To determine safety and tolerability of Palivizumab assessing side effects.

What is known

Cystic Fibrosis Evidence- Based Guidelines for management of infants with Cystic Fibrosis (Borowitz D et al, 2019) suggest that infants with CF could benefit from the use of RSV prophylaxis. Two studies have addressed the use of palivizumab in infants with CF.

A previous chart review (CDSR) of hospitalized infants (Giebels K et al, 2008) found that fewer children who received palivizumab were hospitalized and their length of stay was shorter, although these differences did not reach statistical significance. None of the children who were hospitalized and had received palivizumab had RSV, whereas 42% of those who did not receive palivizumab but were hospitalized were RSV positive. Another paper including data from the Palivizumab Outcomes Registry collecting data of about 20000 infants at risk from year 2000 through 2004 found no hospitalizations over 24 hours in length in 91 patients with CF in which RSV infection was confirmed (Speer ME et al, 2008).

One CDSR (Robinson KA et al, 2016) examined one trial on palivizumab therapy that met the inclusion criteria for analysis. The study, including 186 infants with CF up to two years old, compared a group treated with five monthly doses of palivizumab (n=92) to placebo group (n=94) over one RSV season. Prevention of hospitalization and rate of mortality from RSV were evaluated as primary outcomes. At six months follow-up, one participant in each group was hospitalized due to RSV; there were no deaths in either groups. The overall incidence of adverse events was similar in both groups. As secondary outcomes number of PA) colonizations or change in weight-to-height ratio were evaluated after 12 months of follow-up. Length of stay in hospital, need for intensive care, need and duration for oxygen therapy, nutritional status were not evaluated. Six months after treatment, the Authors reported no clinically meaningful differences in outcomes; however, no data were provided. At 12 months follow-up, there were no significant differences between groups in number of Pseudomonas colonizations or change in weight-to-height ratio. Concerning hospitalization rate associated to palivizumab prophylaxis one observational study reported a hospitalization rate to be higher in the control group. While reductions in mortality rates associated with palivizumab prophylaxis (range from 21% to 78%) were observed in studies of other populations, mortality was not reported as an outcome in studies related to children with CF.

A systematic review evaluated the efficacy of Palivizumab in reducing the incidence of RSV hospitalization in children with CF <2 years of age (Kua KP et al, 2017), including 10 studies that involved 3891 patients with CF from United States, Canada and Europe. Results suggest that Palivizumab may have a potential role in reducing RSV hospitalization in children with CF.

Surprisingly, a PA 1st isolate was significantly earlier in the palivizumab recipient cohort versus non-recipient cohort (median 57 vs. 96 months, P?<?0.025) with a relative risk of 2.5. However, chronic PA infection at 6 years remained low in both groups, with similar lung function and growth parameters (Groves HE et al, 2016).A recently published non-RCT (Buchs C et al, 2017) study concluded that in childern with CF Palivizumab did not delay the acquisition on Pseudomonas aeruginosa and Staphylococcus aureus.

Further, a retrospective study that collected data from CF infants aged <?2 years in Alberta, Canada, from 2000 to 2017 using logistic regression models demonstrated that among a total of 267 CF infants (183 treated with PVZ and 84 untreated with PVZ) PVZ subjects experienced a shorter length of overall stay, both in patients that experienced a respiratory-related illness (RIH) and RSV hospitalizations (Bjornson C et al, 2018).

Consequently to EMA approval Galicia introduced prophylaxis of RSV with nirsevimab into the national immunization program structuring a campaign into 3 groups: (1) risk: children born with risk factors between October 2021 and March 2023 received nirsevimab in the first week of the campaign; (2) catch-up: children born between April and September 24, 2023, received a dose at the beginning of the season and (3) at birth: children born from September 25, 2023 to March 2024 received a dose in the hospital, in the first day of life. Reported data showed that immunization coverage ranges from 85.3% in the catch-up group to 100% of the risk group, with a total of 11,982 immunized children from September 25, 2023 to February 18, 2024. Reports show an 83% reduction in hospitalization rate for RSV in the cohort of catch-up children and 88% in the cohort of infants aged <6 months. This program of immunization started in an Italian Pediatric Center, but fewer patients were elegible according to panish indications. It has to be encoureged a universal immunization program with nirsevimab (Villani A et al, 2024).

Recently (Kuitunen I et al, 2024) a review including previous systematic reviews utilizing meta-analyses of randomized controlled trials and focusing on clinical outcomes and comparing prophylaxis with Palivizumab to placebo concluded that monoclonal antibodies are effective in preventing RSV infections and RSV hospitalizations in preterm infants. However, no effect on mortality was seen in these studies. One meta-analysis focused on CF patients had eight comparisons, but it was underpowered to detect any results.

Unresolved questions

The strength of current evidence is insufficient to allow conclusions on the use of the palivizumab in children with CF for the prevention of RSV infection.

Depending on which rate is assumed, a RCT would need a much higher group sample size to detect a 50% or larger difference in hospitalization rates between palivizumab and placebo groups.

Additional research may define the prophylactic role of this drug.

Keywords

Respiratory Syncytial Virus Infections; Virus;