
Does RSV prophylaxis prevents future recurrent wheeze in preterm infants?

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CONTEXT

Respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is the most frequent cause of bronchiolitis during infancy. Long-term airway morbidity occurs in 30-70% of hospitalized infants with RSV LRTI, which is referred to as post-bronchiolitis wheeze (PBW). Evidence exists that milder forms of RSV LRTI, not requiring hospital admission, are also associated with PBW. The clinical picture of PBW is recurrent episodes of wheezing, generally associated with viral upper respiratory tract infection (URTI).

So far, the potential causal role of RSV infection in the development of recurrent wheeze is debated, but strong empirical evidence is lacking. Wu and Hartert therefore concluded that a randomized clinical trial using RSV prophylaxis was warranted to confirm a causal relationship between RSV infection and recurrent wheeze.

MATERIALS AND METHODS

Study design

This was a multicenter, double-blind, randomized, placebo-controlled MAKI trial.

Outcome

Primary outcome was the total number of parent reported wheezing days in the 1st year of life.

Parents recorded airway symptoms, doctor visits, and the use of airway drugs in a daily log until their infant was 1 year of age.

Secondary outcomes were the number of days with bronchodilator use, the number of RSV infections confirmed by means of a nasopharyngeal swab positive for RSV ribonucleic acid (RNA) with or without medical attention, the number of hospitalizations for laboratory-proven RSV infection, the number of

wheezing episodes, and the prevalence of recurrent wheeze.

- Medical attention was defined as a visit to either a general practitioner or a hospital.
- A wheezing episode was defined as a respiratory episode with wheezing on more than 1 day.
- The interval between two episodes was defined as a period of at least 7 days without respiratory symptoms.
- Recurrent wheeze was defined as three or more episodes of wheezing during the 1st year of life.
- A family history of atopy was defined as a physician diagnosis of asthma, hay fever, or eczema in at least one of the parents.

Population

Inclusion

Healthy preterm infants with gestational age, 33-35 weeks. Aged less than 6 months at the RSV season.

Exclusion

- Congenital heart disease.
- Bronchopulmonary dysplasia.
- Down's syndrome or other serious congenital disorders.
- Infants who required mechanical ventilation at birth, who were treated with surfactant. Physician-diagnosed wheeze before the start of the RSV season.

Intervention

Eligible infants were randomly assigned in a 1:1 ratio to receive either palivizumab at a dose of 15 mg per kg of body weight or placebo during the winter season.

Blinding

This was a blinded study.

Only the administering nurses were aware of the study group assignments, but they were fully trained to reveal no knowledge of the randomization to parents and were not involved in the reporting of data analyses.

Randomization and allocation

The concealment of study group assignment was performed with a randomization list that used a permuted block design, which was generated by an independent pharmacist before the start of the trial. The randomization was stratified according to gestational age.

RESULTS

Four hundred and twenty-nine were enrolled in the study. The two study groups were well balanced on the basis of inclusion year, gestational age, and birth month. Birth weight, family history of atopy, presence of siblings, and

other baseline characteristics were similar, except for sex where there is slightly more male in the treatment group (58% male infants in the RSV prevention group vs 44% in the placebo group).

A median number of 4 injections during the RSV season were administered to infants in the RSV-prevention group (range, 1-5) and the placebo group (range, 2-5). In the RSV-prevention group, 95% of scheduled injections and 89% of follow-up of daily logs were completed, as compared with rates of 92 and 88%, respectively, in the placebo group. The median follow-up duration was 10 months (range, 0-12) in the two study groups.

RSV Infection

Infants who were treated with palivizumab had a lower incidence of RSV-related hospitalization than those treated with placebo (0.9 vs 5.1%, $P = 0.01$) with a number needed to treat of 23. The infants who were treated with Palivizumab also had a lower incidence of medically attended nonhospitalized RSV infection.

Palivizumab treatment resulted in a relative reduction of 61% (95% confidence interval, 56-65) in the total number of wheezing days during the 1st year of life (930 of 53,075 days in the RSV-prevention group (1.8%) vs 2,309 of 51,726 days (4.5%) in the placebo group).

During this time, the proportion of infants with recurrent wheeze was 10% points lower in patients treated with palivizumab (11 vs 21%, $P = 0.01$).

Adverse events

The proportion of patients with serious adverse events was lower in the RSV-prevention group than in the placebo group. There were 32 hospitalizations in 27 children (12.6%) in the RSV-prevention group, as compared with 52 hospitalizations in 47 children (21.9%) in the placebo group ($P = 0.04$).

COMMENTARY

This study has shown in otherwise healthy preterm infants, palivizumab treatment resulted in a significant reduction in wheezing days during the 1st year of life, even after the end of treatment. These findings implicate RSV infection as an important mechanism of recurrent wheeze during the 1st year of life in such infants. The study is thought to be of high quality in our methodological assessment.

Although wheezing is an important sign for parents of preterm infants, the results of this study should be taken with caution. First, the study did not include hard patient oriented outcomes that matters (POEM) such as asthma or

the use of prophylactic steroids/B₂ agonists. Wheezing in an infant could simply be due to the acute RSV infection and it is well known that RSV prophylaxis reduce such an infection even in the highest risk infants.

The study is also funded by industry like so many other RSV prophylaxis studies. It is well known in the medical literature that studies supported by industry are more likely to be positive compared to completely independent investigations.

Prophylaxis is very expensive; therefore a cost-effective study needs to be done. In addition, the cost of such therapy limits its widespread use at the global arena. In addition to the cost, adopting such a therapy is quite cumbersome to parents having to go for regular visits at the hospital in addition to the ethical issue with recurrent intramuscular (IM) injections to administer the therapy.

In conclusion; and although the results of this intervention are quite positive, the application of this intervention to all low risk preterm infants between 33-35 weeks requires positivity at a more solid clinical outcomes such as asthma diagnosis and inhalers' utilization.

Abstracted from

Maarten O. Blanken, M.D., Maroeska M. Rovers, Ph.D., Jorine M. Molenaar, M.D., Pauline L. Winkler-Seinstra, M.Sc., Adam Meijer, Ph.D., Jan L.L. Kimpen, M.D., Ph.D., and Louis Bont, M.D., Ph.D., for the Dutch RSV Neonatal Network *N Engl J Med* 2013;368:1791-9.

REFERENCES

1. Edwards MR, Bartlett NW, Hussell T, Openshaw P, Johnston SL. The microbiology of asthma. *Nat Rev Microbiol* 2012;10:459-71.
2. Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. *Expert Rev Anti Infect Ther* 2011;9:731-45.
3. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: Randomised double blind placebo controlled trial. *BMJ* 2009;338:b897.
4. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. IMPact-RSV Study Group. *Pediatrics* 1998;102:531-7.
5. Mejías A, Chávez-Bueno S, Rios AM, Aten MF, Raynor B, Peromingo E, *et al.* Comparative effects of two neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibodies in the RSV murine model: Time versus potency. *Antimicrob Agents Chemother* 2005;49:4700-7.