

Nirsevimab in Infants: The Cost of Changing the Paradigm

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ABSTRACT

Nirsevimab is an IgG1-type monoclonal antibody approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the prevention of RSV-LRTI in preterm, late preterm, and term infants. Subsequent studies have reported that the efficacy of nirsevimab could be extrapolated to extremely premature children (< 29 weeks gestational age), with chronic lung disease and congenital heart disease. The cost-effectiveness of immunization with nirsevimab appears to be higher than standard care and palivizumab. Despite strong evidence, most countries that have implemented mass immunization programs with nirsevimab are high-income and concentrated in the northern hemisphere.

Keywords: Nirsevimab, Prevention, Respiratory Syncytial Virus, Cost-Effectiveness, Lower Respiratory Tract Infection.

ABBREVIATIONS

RSV: Respiratory Syncytial Virus; RSV-LRTI: Respiratory Syncytial Virus Lower Respiratory Tract Infection.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of respiratory disease in children under 2 years of age each year. Globally, it causes 33 million infections, 3,2 million hospitalizations, and 100 thousand deaths in children under 5 years of age [1]. 90% will have been infected by the time they are two years old. In children younger than 6 months, 45–54% of hospital admissions are due to RSV [2]. Prevention of moderate to severe RSV infection has been a challenge for decades. There are two prevention strategies: i) active immunization ii) passive immunization. Active immunization includes RSV vaccines that have made slow progress from the middle of the last century to the present. Passive immunization involves administering mono or polyclonal antibodies targeting a specific pathogen, which are very useful in children under 6 months of age who cannot produce antibodies independently [3]. The development of passive immunoprophylaxis began in 1992 with the approval of intravenous immunoglobulin against RSV (RespiGam™) that contained polyclonal antibodies with high-titer RSV neutralizing activity that, when administered to children under 2 years of age, decreased hospitalization, severe infection, and intensive care days due to RSV. It was followed by a humanized monoclonal antibody targeting site II of the RSV F protein called Palivizumab (Synagis™–AstraZeneca), which

Vol No: 09, Issue: 01

Received Date: March 18, 2024

Published Date: April 02, 2024

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Citation: Vidal A. (2024). Nirsevimab in Infants: The Cost of Changing the Paradigm. Mathews J Pediatr. 9(1):35.

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until a few years ago was the only approved treatment for the prevention of RSV lower respiratory tract infection (RSV-LRTI), especially in the group of infants with a history of prematurity or bronchopulmonary dysplasia. Later, a second generation of antibodies appeared that had greater affinity for the RSV F protein, whose advantage was the longer duration and a single administration dose such as Motavizumab (Numax™–MedImmune, Inc.) and Suptavumab (Regeneron Pharmaceuticals, Inc.), but were subsequently discontinued due to an increase in skin hypersensitivity reactions (Motalizumab) or lack of efficacy in preventing hospitalization (Suptavumab) [4]. In October 2022, the European Medicines Agency (EMA) approves Nirsevimab (Beyfortus® AstraZeneca/Sanofi Pasteur) for the prevention of RSV-LRTI in neonates and infants during their first RSV season [5]. Subsequently, in July 2023, the Food and Drug Administration (FDA) approves it for the prevention of RSV-LRTI in children less than 24 months of age [6]. The purpose of this review was to review the clinical studies that led to the authorization of the prescription of nirsevimab and the results after its approval.

METHOD

A review of the scientific evidence was carried out with the studies mentioning the word Nirsevimab. The search for articles was carried out in March 2024 in the databases Medline (PubMed), Web of Science (WOS), EBSCO Host, Science Direct, and SCOPUS. MeSH terms and free terms were used in their English versions. The terms were grouped into three dimensions: i) Nirsevimab ii) RSV iii) prevention. The Boolean operator was used “and” to integrate the three dimensions.

Characteristics of Nirsevimab

Nirsevimab is an IgG1-type monoclonal antibody that binds to the prefusion conformation of the RSV F protein, a glycoprotein involved in the membrane fusion step of the viral entry process, and inhibits the fusion of the RSV and the respiratory epithelium, thereby inhibiting viral entry into the cell, and is equally effective against both RSV A and RSV B. It is administered intramuscularly in a single dose for the entire RSV outbreak season. Infants under 5 kg receive 50 mg (0.5 ml from the syringe) and those over 5 kg receive 100 mg (1 ml from the syringe). Some side effects include skin reactions and pain at the puncture site. It should not be administered to children with severe hypersensitivity reactions to active ingredients or excipients of nirsevimab due to the risk of anaphylaxis, which is also described with the use of other monoclonal antibodies or other human immunoglobulins IgG1 [7].

Preapproval clinical studies

The first study considered was multicenter and carried out with patients from the northern and southern hemispheres. 1453 infants with a history of prematurity (29 weeks 0 days to 34 weeks 6 days of gestation) were enrolled. 969 of them received nirsevimab 50 mg intramuscularly in a single dose and the remaining 484 received a placebo, and a 150-day follow-up was carried out during the RSV season. The incidence of RSV-LTRI was 70.1% lower (95% CI, 52.3 to 81.2; $p < 0.001$) and the incidence of RSV-hospitalization was 78.4% lower (95% CI, 51.9 to 90.3; $p < 0.001$) in nirsevimab group. Adverse effects were similar in the nirsevimab and placebo groups and no anaphylaxis or severe hypersensitivity reactions were reported. The authors concluded that in infants with a history of prematurity, immunoprophylaxis against RSV with nirsevimab was effective in reducing RSV-LTRI and RSV hospitalization during a typical RSV season (5 months) with a good safety profile [8]. The second study was conducted on infants with a history of being born with a gestational age of 35 weeks or more, who were less than 1 year old and were facing their first RSV season. 1490 infants were included, 994 received Nirsevimab, and 495 received placebo. In the group that received nirsevimab the RSV-LTRI fell by 74.5% (95% CI, 49.6 to 87.1; $p < 0.001$), and hospitalizations by 62.1% (95% CI, 8.6 to 86.8; $p = 0.07$). The authors concluded that the administration of a single dose of nirsevimab in healthy late preterm and term infants provides protection against RSV-LTRI [9]. A meta-analysis that grouped these two studies to determine the clinical benefit, highlighted the importance of not having higher rates of adverse effects than placebo, but recommended future cost-effectiveness studies [10].

Post-approval clinical studies

A controlled study in 2350 infants compared the nirsevimab group ($n = 1564$) with the placebo group ($n = 786$). In this study, an analysis was carried out by pharmacokinetic extrapolation that allowed us to demonstrate that the efficacy of 1 dose of nirsevimab found in healthy term or preterm infants (≥ 29 weeks gestational age) are similar to the groups of children with extreme prematurity (< 29 weeks gestational age), chronic lung disease, congenital heart disease [11]. In children with chronic lung disease or congenital heart disease, a study was carried out that showed that a dose of 200 mg of nirsevimab administered before exposure to the second season of RSV has a safety profile and efficacy similar to the schedule of 5 monthly doses of palivizumab, therefore which could be an effective strategy in this group of high-risk children [12]. In healthy infants ≥ 35 weeks of gestational age who received nirsevimab in their first season

of RSV, their clinical evolution was studied in the second season of RSV, and it was found that there was no increase in the incidence, severity of RSV-LTRI or evidence of antibody-dependent enhancement of infection [13]. Spain was one of the first countries in Europe to introduce nirsevimab to the public immunization program, achieving average coverage of 90% for the target population during the first 3 months. Therefore, the analysis of the results in Spain reflects what happens in real life. In the regions of Spain (Murcia, Valencia, Valladolid) in which infants received nirsevimab, an average efficacy of 84.4% was found to reduce hospitalization due to RSV-LTRI [14].

Cost-effectiveness studies

A cost-effectiveness model for palivizumab carried out in the USA with premature infants from 29 to 34+6 weeks of gestation without risk conditions, showed that it costs \$9,572 and \$9,584 US dollars more (health and social perspective, respectively), than standard care (without prophylaxis), which does not make it cost-effective. When applying this same model with nirsevimab, it is estimated that it could be cost-effective, if the price is below \$1923 and \$1962, from a health and social perspective, respectively [15]. Cost-effectiveness analyzes carried out in high-income OECD countries (USA, Canada, England, and Wales) show that nirsevimab is less expensive and clinically more effective than the previous immunization program with palivizumab. However, cost-effectiveness may vary in the different regions modeled and will depend on the costs of nirsevimab for each country, the source of the clinical effectiveness data, and the severity of the RSV epidemic [16]. A multi-criteria decision analysis (MCDA) was recently applied in Spain, which consists of a step-by-step, systematic, and transparent multidimensional measurement structure. A multidisciplinary committee of 9 experts participated in this evaluation, who applied 26 criteria to evaluate the clinical impact of nirsevimab in the prevention of RSV in neonates and infants. The evaluation summary indicated that nirsevimab adds value to the prevention of RSV in newborns and infants during their first RSV season in Spain, compared to placebo, both due to its effectiveness and its solid safety profile. Furthermore, the committee noted that expanding the age range for the administration of nirsevimab could bring greater economic and social benefits [17]. A cost-effectiveness study carried out in Ontario Canada with infants with values adjusted to Canadian dollars compared two strategies: immunization with nirsevimab to an entire population of infants vs protein-based maternal vaccine (RSVpreF) plus nirsevimab only to infants with high risk of RSV-infection. The authors conclude that both strategies

may have social profitability, but the annual cost may be much higher if nirsevimab is administered to all infants (\$10.6 million Canadian dollars) than the combined strategy (\$6.3 million) which could be more cost-effective [18]. Cost-effectiveness analyzes are even more important in low- to middle-income countries. An example of this is Vietnam, a country that analyzed cost-effectiveness based on different spending thresholds of its gross domestic product (GDP), demonstrating the RSV prevention strategy with the most favorable cost-effectiveness would need to be priced at \$5/dose or less to achieve a greater than 95 % probability of being cost-effective [19].

Geographical inequalities

Despite the evidence previously presented, not all continents are advancing with the same speed in the incorporation of nirsevimab since only some countries have incorporated it into public health programs. For example, in Europe (the first continent to approve it) there are still disparities in its administration that have to do with bureaucratic obstacles in some countries because they want to wait for cost-effectiveness studies to apply to the population [20]. On the other hand, low- and middle-income countries are historically 15 to 20 years behind in the implementation of immunization strategies compared to high-income countries and are unfortunately very dependent on non-governmental organizations or philanthropists [21]. An exception that should be imitated is Chile, a country that was one of the first in the world to begin mass vaccination against COVID-19 during the pandemic [22], and that will now be the first in Latin America to apply nirsevimab free of charge for the entire population of infants under 6 months of age who will face the RSV epidemic in 2024 [23].

CONCLUSIONS

Nirsevimab is an effective and safe monoclonal antibody to reduce RSV-LTRI and hospitalizations due to RSV in term infants, premature infants, and risk conditions such as chronic lung disease, and congenital heart disease. Its cost-effectiveness appears to be higher than in children without immunoprophylaxis and even in those who receive palivizumab. Despite the robust evidence available, currently, access to this immunization strategy is largely concentrated in high-income countries in the northern hemisphere.

CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest to declare.

FUNDING SOURCES

The author has no relevant financial or non-financial interests to disclose.

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