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Immunoprophylaxis against Respiratory Syncytial Virus Infections

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Abstract

Respiratory Syncytial Virus is an etiological cause of lower respiratory tract infections. Due to the controversial therapeutic approach, it has a significant share in the causes of hospitalizations and even fatal outcomes concerning children up to two years of age. The elderly patients, especially the immune compromised and those with co-morbidities, are at a great risk of developing severe conditions because it is often not considered as pathogen. Those are the reasons which determine the necessity of prophylaxis of the abovementioned target groups of patients - children up to two years of age and adults over 65 years of age.

The aim of this review is to analyze the options of immunoprophylaxis against Respiratory Syncytial Virus-polyclonal immunoglobulin, monoclonal antibodies and vaccines.

Keywords: RSV; Monoclonal Antibodies; Vaccines

Introduction

Respiratory Syncytial Virus (RSV) is a RNA virus which causes respiratory tract infections. The name stems from the characteristic histopathological finding of syncytia observed in tissues [1,2]. RSV was primarily identified in 1955 as a cause of chimpanzee coryza and a year later it was isolated from infants with respiratory infections in the US [3]. Since then, up until present days, RSV has been the most common pathogen causing viral bronchiolitis in infants and accountable for 59-80% of the acute bronchiolitis cases in children up to two years of age [4-6]. The burden of acute lower respiratory tract infections due to RSV is estimated to be equal to 3.2 million hospital admissions globally and 55,000 to 199,000 lethal outcomes in children up to five years of age. Report that the death rates may even rise up to 7-40% [7] and the reason for this wide range is due to disparity in the definitions and the therapeutic strategies used in different publications.

Authors report severe cases of RSV respiratory infection in adults, particularly in elderly patients and the ones with cardiopulmonary or immunodeficiency co-morbidities. Data of mortality in adults are contradictory since the disease is commonly unrecognized and RSV is often not considered as a cause [8].

The significant rate and severity of RSV infections provide strong rationale of effective prophylaxis both in infants and elderly patients to prevent the negative health and economic outcomes of the disease.

Search Selection

We have reviewed the literature for randomized placebo-controlled trials showing the efficacy, advantages, disadvantages and side effects of polyclonal immunoglobulin, monoclonal antibodies and vaccines in infants and elderly people, as well as, meta-analyses comparing them and guidelines with recommendations for RSV prophylaxis. Keywords and extensive vocabulary related to RSV, immunoprophylaxis, monoclonal antibodies, polyclonal immunoglobulin, monoclonal antibodies, vaccines, infants, elderly people.

Virology

RSV is a RNA virus within the Pneumovirus genus of paramyxovrisuses [9]. It consists of a genome with a single-stranded negative-sense RNA which encodes ≥11 proteins and an envelope with transmembrane surface glycoproteins G and F with attachment and fusogenic properties, respectively [1,2]. The infection initiates with glycoprotein G binding to a host-cell receptor, which is possibly a heparin-like glycosaminoglycan. This is followed by the glycoprotein F- mediated fusion of viral and cell membranes and the penetration of the viral nucleocapsid into the host-cell cytoplasm [10]. Glicoproteins G and F initiate the production of virus-neutralizing antibodies in the host, as well. RSV lacks neuraminidase and hemagglutinin glycoproteins [1,2].

Two main subtypes of RSV have been identified - A and B with 11 and 23 genotypes, respectively. The main antigenic and genomic differences between and within the subtypes are mainly based on variations of glycoprotein G, while glycoprotein F remains relatively stable. Due to this the antibody response of the host to the RSV infection is cross-reactive to glycoprotein F of both subtype A and B, while is highly specific to glycoprotein G of each subtype and even of the subtype variations [10-12].

Immunoprophylaxis

Polyclonal Immunoglobulins

RSV immune globulin intravenous (RSV IG-IV, RespiGam) is a polyclonal immunoglobulin derived from human plasma with high circulating levels of anti-RSV neutralizing antibodies which has been licensed by the Food and Drug Administration (FDA). It is administered intravenously, monthly, for 5 months [13,14]. The PREVENT study in 1997 demonstrated a reduction of hospi-

talizations incidence by 41%; a decrease by 61% in the days with increased oxygen requirement, as well as, a shortening by 51% in terms of total hospital days for respiratory illness [15]. On the other hand, RSV IG-IV is contraindicated for children with cyanotic congenital heart disease (CHD) because of the increased risk of cyanotic episodes and the poor outcome after surgery, probably due to hyperviscosity [16]. The product was withdrawn from the market in 2004 due to its multiple disadvantages - the intravenous infusion administration which demands monthly hospital admissions and leads to fluid overload in 1-3% of the cases, the risk of transmission of blood-borne pathogens, the alteration of the immunization schedule - the measles-mumps-rubella and other live vaccines should be delayed with 10 months because of possible interfering and last, but not least, it is not considered as cost beneficial [17-21].

ADMA Biologicals' RI-001 is another polyclonal immunoglobulin derived from human plasma with high circulating levels of anti-RSV neutralizng antibodies. The product is reported to be effective in both immunocompetent and immunocompromised animal models. A Phase-II clinical trial showed a significant increase in the neutralizing antibodies titers - ≥ fourfold, as well as its safe profile [22,23].

Monoclonal Antibodies

Palivizumab is the only approved product for prophylaxis of RSV in children. It is a humanized IgG monoclonal antibody developed through recombinant DNA technology and binds to glycoprotein F of both subtypes A and B RSV. It does not prevent infection but prevents severe respiratory illness caused by RSV. By being a specific monoclonal antibody it has no protective effect against other respiratory viruses [1]. The main benefit of Palivizumab among others refers to the reduction in the hospitalization incidence caused by RSV (55-78%), but neither of the authors [24,25], nor the American Association of Pediatrics (AAP) have reported reduction in mortality [24-27]. Apart from the reduction in the hospitalization incidence of infants born at 35 weeks' gestation or earlier, as well as children up to 24 months of age with diagnosed bronchopulmonary dysplasia (BPD), the IMpact-RSV Study reports significant reduction in the duration of in-hospital stay and lower incidence of admission in pediatric intensive care unit (PICU) [27]. Other advantages of Palivizumab stem from its safety profile and the lack of interference with the immunization schedule. By being a recombinant product, it has no potential for transmitting blood-borne pathogens and the intramuscular administration may be performed in an outpatient setting, without any risk of fluid overload [21]. Nevertheless, prophylaxis of Palivizumab is restricted as it is used only for certain risk group patients and by being administered monthly it has high cost. Cost--effectiveness analyses show that the healthcare systems would not save financial resources if all children receive prophylaxis with the product although those analyses do not consider some of the RSV infections' long-term effects (recurrent "wheezing", bronchial asthma), which are of social significance [1,21].

Given its benefits, AAP developed guidelines on Palivizumab. The 2006 guideline recommends its administration in five monthly doses of 15mg/kg, starting from November and covering the groups of children stated in the Report of the Committee on Infectious Diseases. [28,29] They are summarized in Table 1.

According to the 2014 guideline, concerning the prophylaxis with Palivizumab, the AAP provides a definition of BPD/ chronic lung disease (CLD) of prematurity - requirement for 28 days of more than 21% oxygen beginning at birth. As for the preterm infants, those born at 28 weeks' gestation + 6 day are recommended to be provided with prophylaxis. The AAP recommends selected infants with neuromuscular disease or congenital anomaly, which impairs their ability to clear secretions from the lower airways, to be considered for prophylaxis during the first year of life, as well [30].

An international group of specialists in the field published in 2017 recommendations concerning the use of Palivizumab in children with CHD. The target groups include children with hemodynamically significant CHD cyanotic, with pulmonary hypertension, with symptomatic airway abnormalities; children up to one year of age with cardiomyopathies, requiring treatment; children with surgically treated CHD and hemodynamically significant residual problem, children up to two years of age in the 6-month postoperative period [31].

In Bulgaria, the populations of children, who are administered Palivizumab, are determined by the National Health Insurance Fund (NHIF) - children born premature with BPD, children born premature with low or extremely low weight at birth and children with CHD [32].

Guideline/Recommendations	Patient group
AAP (2006) (29)	1. Children < 24 months of age with CLD of prematurity who have required medical therapy (supplemental oxygen, bronchodilator or diuretic or corticosteroid therapy) for CLD within 6 months before the start of the RSV season.
	2. Infants without CLD born at ≤ 28 weeks of gestation < 12 months of age during their first RSV season
	3. Infants without CLD born at 29 to 32 weeks of gestation gestation < 6 months of age during their first RSV season
	4. Infants between 32 and 35 weeks of gestation only if two or more of these risk factors are present :
	- child care attendance
	- school-aged siblings
	- exposure to environmental air pollutants
	- congenital abnormalities of the airways
	- severe neuromuscular disease
AAP (2014) (30)	1. Infants with a gestational age of ≤28 weeks, 6 days < 12 months at the start of the RSV.
	2. Infants and children <12 months who develop CLD of prematurity
	- < 24 months of age if continue to require supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy within 6 months of the start of the RSV season
	3. Infants with CHD < 12 months at the start of the RSV
CHD and respiratory syncytial virus: global expert exchange recommendations (2017r) (31)	1. Children < 2 years of age with hemodynamically significant CHD
	-cyanotic
	-with pulmonary hypertension
	-with symptomatic airway abnormalities
	2. Children up to one year of age
	-with cardiomyopathies, requiring treatment
	- with surgically treated CHD and hemodynamically significant residual problem
	3. Children < 2 years of age in the 6-month postoperative period
NHIF (2019) (32)	1. Infants and children born premature with CLD:
	- ≤ 28 weeks of gestation < 12 months of age
	- 29-35 weeks of gestation < 6 months of age

- ≤ 35 weeks of gestation < 24 months of age if treated with supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy the previous 6 months
2. Infants and children born premature with low or extremely low weight at birth:
-≤ 30 weeks of gestation with extremely low (≤ 999rp) or low (1000-2499rp) weight at birth < 12 months of age at the start of the RSV.
->30 ≤ 32 weeks of gestation c with extremely low (≤ 999rp) or low (1000-2499rp) weight at birth < 6 months of age at the start of the RSV.
3. Children with CHD:
-CHD left-to-right shunt
-complex CHD
-obstructive CHD

Table 1: Summary of the groups recommended for prophylaxis with Palivizumab

Niversimab is another product - a recombinant humanized IgG1 monoclonal antibody which binds to RSV's glycoprotein F. It has a modified Fc region through the YTE technology a substitution of three amino acids, which extends its half-life. Thus, it is administered once and provides protection for 5 months, as long as it is the RSV season, which reduces the cost makes its cost lower and delivers an opportunity for use in wider populations. The safety and efficacy of Niversimab are reported in two randomized, double-blinded, placebo-controlled multicenter trials in Phase II b and Phase III (MELODY), respectively. They were conducted on 2,350 infants born term and preterm at ≥ 29 weeks of gestation during their first RSV season, who received one dose of Nirsevimab or placebo. Infants with BPD and CHD were excluded. RSV was identified as a pathogen through PCR technology. As criteria for efficacy, the mentioned trials used the incidence of medically attended RSV low respiratory tract infections (MA RSV LRTI), of hospitalizations due to MA RSV LRTI and of very severe MA RSV LRTI (requirement for supplemental oxygen or intravenous fluids) through 150 days after dosing. The trials demonstrated efficacy of the product, since all of the abovementioned conditions were found only in 1% of the infants dosed with Niversimab [33].

Concerning the risk groups for severe RSV infections infants born preterm at < 29 weeks of gestations, those with CLD or CHD of prematurity the MEDLEY study Phase II/III reports better inhibitory effect both in vitro and in vivo of Nirsevimab compared to Palivizumab Niversimab reduced the incidence of MA RSV LRTI to 0.6% while Palivizumab to 1% [34].

Motavizumab, created through remodeling the heavy and light chains of Palivizumab and Mota-YTE, created from Motavizumab through the YTE-technology are other monoclonal antibodies developed for RSV prophylaxis. Mota-YTE showed extended half-life up to 100 days in healthy adult volunteers. In clinical trials conducted on infants, Motavizumab showed identical to Palivizumab pharmacokinetic profile and rate of antidrug antibodies development. When tested in children with hemodynamically significant CHD, the results of Motavizumab were comparable to Palivizumab. Moreover, because of the large number of adverse effects, mostly cutaneous, the FDA has not authorized the production of Motavizumab [35].

Suptavumab is another monoclonal IgG1 antibody against glycoprotein F of RSV, which appeared to be more potent than Palivizumab in vitro and with similar safety profile to placebo in adult volunteers. A phase III study was conducted on 1,158 infants, who did not have access to Palivizumab and received 1 or 2 intramuscular doses of Suptavumab. The drug did not show reduction in the incidence neither of hospitalizations, nor of RSV low respiratory tract infections (RSV LTRI). A new strain of RSV B with two amino acid mutations in the Suptavumab epitope, unresponsive to this antibody, was found as a probable reason. Due to this, the work on Suptavumab was discontinued in 2017 [35,36].

Regardless, during the current year Sun et al conducted systematic review and meta-analysis on 15 randomized clinical trials with 18,395 participants to compare the safety and efficacy of Palivizumab, Motavizumab, Nirsevimab and Suptavumab. The results have shown low-to-moderate certainty evidence for reduction in the hospitaliztions incidence, as well as moderate-to-high certainty evidence for reduction in the incidence of RSV infections for Palivizumab, Motavizumab and Nirsevimab. Palivizumab and Motavizumab have reduced both the incidence of hospitalizations in PICU and the usage of supplemental oxygen with Motavizumab having advantage, while Niversimab has reduced only the usage of supplemental oxygen. No differences concerning the safety profile of the products have been reported but the authors have not compared each adverse effect [37].

No differences between the monoclonal antibodies, mentioned in this review, concerning the comparison of patients with or without co-morbidities were reported [37].

Vaccines

Developing RSV vaccine has been declared a priority by the Initiative of Vaccine Research of the World Health Organization (WHO). As of today, no vaccine has been approved but scientists make endeavor to develop vaccines which target elderly people over 65 years of age and pregnant women and through transplacental transmission of antibodies to protect their infants during the first six months of their lives.

The first attempt in this field was the formalin-inactivated pediatric vaccine in 1960s, which led to an increase in hospitalization incidence among the vaccinated infants due to enhanced disease during subsequent infection, as well as to lethal outcomes in two cases [38].

After the bitter experience, attempts to develop live-attenuated vaccines have been made because of the expected advantages-intranasal administration and the theoretical assumption that it would not lead to enhanced disease in naïve infants during subsequent infection. These expectations have not been met so far because of the higher than desirable virus shedding titers, instability, restricted antibody response and even higher incidence of MA RSV LRTI [39-41]. In spite of that, there are live-attenuated candidates for prophylaxis of infants under development in Phase I trials [42,43].

RSV-preF is a RSV vaccine candidate from Pfizer Inc. declared accepted for priority review by the FDA. The decision is expected in May 2023. It is a bivalent vaccine based on the structure of glycoprotein F in its prefusion conformation (pre-F). The aim to produce prefusion-specific antibodies which by binding to glycoprotein F would lock it in its prefusion conformation and thus would prevent the fusion of viral and cell membranes. RENOIR Phase III trial reported 85.7% efficacy in elderly patients over 65 years of age and when administered to pregnant women concerning their infants – 81.8% efficacy until the first 90 days of their lives and 69.4% until six months of age [45, 46].

RSV OA is a candidate from GSK for adults ≥ 60 years of age. It is a monovalent vaccine, containing pre-F subunit combined with adjuvant, which induces strong antibody-mediated and cell immune responses. AReSVi-006 Phase III trial shows 71.7% to 94.1% efficacy regardless of co-morbidities, as well as safe profile [47].

Bavarian Nordic MVA-BN RSV is a recombinant vaccine containing five different antigens under development for RSV prophylaxis of elderly people. It induces broad and sustained antibody, cell and mucosal immune response and has an acceptable safety profile. Results from Phase III trial are expected [48].

Concerning patients with co-morbidities only AReSVi-006 Phase III trial reports effect comparable to that in patients without co--morbidities. We could not find statements in the literature in terms of comparison between patients with or without co-morbidities neither between other vaccine candidates, nor between monoclonal antibodies and vaccine candidates.

Conclusion

By causing lower respiratory tract infections Respiratory Syncytial Virus appears to be of medical and social significance for elderly adults over 60 years of age and children up to two years of age, especially those with bronchopulmonary dysplasia and congenital heart disease. Given the documented adverse effects and disadvantages of intravenous immune globulin, monoclonal antibodies are a leading form of RSV immunoprophylaxis. Palivizumab is currently the only licensed monoclonal antibody with documented efficacy used for prophylaxis of children up to two years of age but it is restricted only in certain risk groups due to the monthly administration and high cost. However, Niversimab is a promising candidate under development with proven better inhibitory effect than Palivizumab and by being administered only once during the RSV season, it could expand prophylaxis coverage. Developing RSV vaccine has been declared as a priority by the Initiative of Vaccine Research of the World Health Organization. Currently, there are candidates with a safe profile and good efficacy in Phase III trials concerning the prophylaxis of adults over 60 years of age and infants up to six months of age by being administered during pregnancy.

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