Implementation of monoclonal antibodies against seasonal outbreaks of respiratory syncytial virus: impact on incidence and mortality

Anticuerpos monoclonales contra brotes estacionales de virus sincitial respiratorio: impacto en tasas de incidencia y mortalidad

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Abstract

Acute lower respiratory infections (ALRI) in children under 5 years old represent a significant cause of morbidity and mortality worldwide, particularly in low- to middle-income countries. ALRI may be caused by numerous microorganisms, with viruses being the most frequent culprits. Preventive measures have been taken to decrease the incidence and mortality of the most prevalent causative agents, namely respiratory syncytial virus (RSV), influenza A and B, and some adenoviral subtype. Nonetheless, only the vaccines for type A and B influenza are currently available and recommended for use in children. Among these viruses, RSV stands out as the leading cause of ALRI and is also responsible for a significant proportion of hospitalizations related to bronchiolitis and pneumonia. Another distinctive aspect of RSV is its seasonal pattern, typically peaking during colder months in temperate regions, and during the rainy season in tropical areas. Given its predictive epidemiological behavior, other measures have been developed to decrease its incidence and morbimortality during this specific timespan. Available evidence of high and moderate certainty has shown that monoclonal antibodies (mAbs) significantly reduce the rates of RSV infection as well as the need for hospitalization, need for ICU admission, and RSV-associated mortality. Motavizumab, nirsevimab, palivizumab, and suptavumab are some of the available alternatives to decrease the global impact of RSV and ALRI. The aim of this review is to analyze the mechanism of action of mAbs to decrease the burden of RSV in children's health, analyzing primary outcomes such as mortality, hospital admissions, and ICU admissions; moreover, financial aspects will also be discussed.

Keywords: Acute lower respiratory infections, respiratory syncytial virus, monoclonal antibodies, child mortality, public health.

Resumen

Las infecciones respiratorias agudas bajas (IRAB) en niños menores de 5 años representan una causa significativa de morbilidad y mortalidad en todo el mundo, particularmente en los países de ingresos bajos y medianos. Las IRAB pueden ser causadas por numerosos microorganismos, siendo los virus los culpables más frecuentes. Se han tomado medidas preventivas para disminuir la incidencia y mortalidad de los agentes causales más prevalentes, como el virus respiratorio sincitial (VRS), los virus de la influenza A y B, y algunos subtipos de adenovirus. No obstante, actualmente solo las vacunas contra la influenza de tipo A y B están disponibles y se recomiendan para su uso en niños. Entre estos virus, el VRS se destaca como la principal causa de IRAB y también es responsable de una proporción significativa de hospitalizaciones relacionadas con bronquiolitis y neumonía. Otro aspecto distintivo del VRS es su patrón estacional, alcanzando su punto máximo generalmente durante los meses más fríos en las regiones templadas y durante la temporada de lluvias en las zonas tropicales. Dado su comportamiento epidemiológico predecible, se han desarrollado otras medidas para disminuir su incidencia y la morbimortalidad durante este período específico. La evidencia disponible, de alta y moderada certeza, ha demostrado que los anticuerpos monoclonales (mAbs) reducen significativamente las tasas de infección por VRS, así como la necesidad de hospitalización, ingreso a la UCI y la mortalidad asociada al VRS. Motavizumab, nirsevimab, palivizumab y suptavumab son algunas de las alternativas disponibles para disminuir el impacto global del VRS y las IRAB. El objetivo de esta revisión es analizar el mecanismo de acción de los mAbs para reducir la carga del VRS en la salud infantil, analizando resultados primarios como la mortalidad, las hospitalizaciones y los ingresos a la UCI; además, también se discutirán los aspectos financieros.

Palabras clave: Infecciones respiratorias agudas bajas, virus respiratorio sincitial, anticuerpos monoclonales, mortalidad infantil, salud pública.

Introduction

Acute lower respiratory infections (ALRI) in children under 5 years old represent a significant cause of morbidity and mortality worldwide, particularly in low- to middle-income countries. In 2019, 33 million ALRI associated with respiratory syncytial virus (RSV) associated were reported, as well as 3.6 million RSV-associated hospital admissions and over 100.000 deaths in children under 5 years of age[1]. Globally, ALRI accounted for nearly 15% of all deaths in this age group, making them one of the leading cause of preventable child mortality[2]. Moreover, the economic burden of ALRI is colossal, considering hospitalization costs, prolonged treatment durations, and the need for intensive care unit (ICU) in severe cases, leading to severe straining of the public health systems. Research by Martinón-Torres et al.[3] in Spanish children reported that nearly €87 million are spent yearly when considering only the RSV-associated costs. Notably, the financial burden may be higher, as the above estimate does not consider the parental income loss due to caregiving or other indirect expenses.

The panel of etiologic agents causing ALRI includes numerous microorganisms; however, viruses represent most of it. Preventive measures have been taken to decrease the incidence and mortality of the most prevalent causative agents, namely RSV, Influenza A and B, and some adenoviral subtypes[4]. Nonetheless, only the vaccines for type A and B influenza are currently available and recommended for use in children[5]. Among these viruses, RSV stands out as the leading cause of ALRI and is also responsible for a significant proportion of hospitalizations related to bronchiolitis and pneumonia[6]. Another distinctive aspect of RSV is its seasonal pattern, typically peaking during colder months in temperate regions, and during the rainy season in tropical areas. Given its predictive epidemiological behavior, other measures have been developed to decrease its incidence and morbimortality during this specific time-span[7].

Available evidence of high and moderate certainty has shown that monoclonal antibodies (mAbs) significantly reduce the rates of RSV infection as well as the need for hospitalization, need for ICU admission, and RSV-associated mortality[8]. Motavizumab, nirsevimab, palivizumab, and suptavumab are some of the available alternatives to decrease the global impact of RSV and ALRI. The aim of this review is to analyze the mechanism of action of mAbs to decrease the burden of RSV in children's health, analyzing primary outcomes such as mortality, hospital admissions, and ICU admissions; moreover, financial aspects will also be discussed.

MECHANISM OF ACTION OF MONOCLONAL ANTIBODIES

The mechanism of mAbs lies in a form of passive immunity by targeting specific viral proteins to neutralize the pathogens and prevent uncontrolled replication[9]. In the case of RSV, most mAbs focus on the viral fusion (F) protein, the main component that allows RSV to enter host cells and initiate replication. Neutralizing the F protein results in decreased replicability; thus, halting the pathogen's virulence[10]. Since antibodies are introduced directly, maximum efficacy is achieved almost immediately; however, the protection is only temporary given that antibodies are progressively eliminated from the system[11]. In contrast, vaccines act through active immunity, providing long lasting endogenous antibody production but the effect's onset is relatively slower. Nonetheless, to date there is no effective vaccine against RSV in children, currently making mAbs the most effective available therapy[12].

Palivizumab, one of the earliest approved mAbs against RSV, showed significant utility for reducing RSV infections in preterm infants, hospitalization from any respiratory disease, and other ICU-associated variables, although mortality remained the same[13]. Recent advancements in mAbs technology have allowed the development of long-acting antibodies with a wider array of benefits in contrast to its predecessors. Namely, Nirsevimab has been engineered to have an extended half-life, providing protection across the full length of the RSV season with a single dose. Moreover, Nirsevimab has been shown to decrease lung inflammatory response through other non-Fc-effector functions. Although the exact mechanisms are unknown, it is presumed that these features lead to improvement in other variables, such as ICU length-of-stay, oxygen requirement, need for mechanical ventilation and mortality rates, in contrast to palivizumab[14,15].

IMPACT OF MONOCLONAL ANTIBODIES IN RESPIRATORY SYNCYTIAL VIRUS OUTCOMES

Several variables are taken into account to measure the impact of any therapeutic measure regarding disease outcomes. The most widely analyzed parameter to determine effectivity is mortality rate. RSV accounts for almost 4% of all deaths between 28 days and 6 months old infants. Furthermore, the mortality rate in infants ranges from 1 to 8% of all infected patients, depending mostly on risk factors such as prematurity, low birth weight, and congenital heart disease[1,16,17]. Measuring the impact in mortality due to RSV infections has been quite challenging in high-income countries since the mortality in those places is already relatively lower due to improved access to healthcare. However, in-hospital mortality in low- to middle-income countries has decreased significantly in the last decade going from 1% overall mortality in 2012 to 0.5% after the implementation of mAbs. Therefore, evidence has shown that usage of mAbs statistically doubles the chance of in-hospital survival of RSV patients[1,18].

On the other hand, incidence is another relevant parameter when it comes to communicable diseases such as RSV infections. Incidence reduction is, most likely, the most notorious parameter when it comes to showing the effectiveness of the implementation of mAbs. Along these lines, clinical trials of palivizumab and nirsevimab have shown a significant decrement in RSV infection rates, particularly in premature infants and those with comorbidities[19,20].

For instance, research carried out by Mazagatos et al.[21] estimated that a single nirsevimab dose would prevent nearly 10,000 cases, corresponding to a 75% incidence reduction. Likewise, López-Lacort et al. reported that assuming a constant effectiveness during 5 months, nirsevimab would prevent between 5,121 and 8,846 RSV bronchiolitis per 100,000 infants, amounting to an incidence reduction of 80%. Furthermore, decreasing the number of primary infections also directly decreases the viral load within the community; thus, making a broader contribution to the public health benefit and herd immunity effect in high-risk areas[22].

Moreover, need for hospitalization is another great predictor for complications and mortality. Available evidence has shown that nirsevimab provides an enormous protection against hospitalization in those receiving a single dose during peak season. The adjusted effectiveness in preventing hospitalization due to RSV infection is about 93.6% at 30 days and then gradually decreases, with a reduced effectiveness to 87.6% at 150 days[23]. The overall conclusion of several studies is that despite this time-dependent decreasing trend, nirsevimab is an effective measure for reducing the in-hospital burden of RSV infections. Other studies have reported lower impact in hospitalization rates ranging from 70 to 80% reduction, which is not minor. However these studies involve smaller samples, only short-term follow-ups and an overall lower quality methodology in contrast to previous studies[24,25].

Another critical aspect regarding RSV infections is the need for ICU admission. In general, RSV mortality in the pediatric ICU (PICU) is variable, but trends towards the higher end. Available epidemiological data suggest that RSV-associated PICU mortality ranges from 5 to 10% of all admitted patients[26]. A multi-center, double-blind trial studied infants who were 12 months of age or younger, had been born at a gestational age of at least 29 weeks, and were entering their first RSV season. A single nirsevimab dose was randomly assigned at a 1:1 ratio, to analyze need for hospitalization and need for ICU admission as a secondary endpoint. Very severe RSV-associated ALRI occurred in 0.1% of the nirsevimab group, in contrast to 0.5% of the control group showing an efficacy of 75.7% (95% confidence interval, 32.8 to 92.9; P=0.004)[27].

In addition to the overall healthcare impact of mAbs in RSV infections, the relief of the financial burden is not negligible. Reduction in the need for hospitalization, ICU

admissions, mechanical ventilation, shorter in-hospital stays, and less unpaid days for family caregivers translates to lower financial damage. Economic analyses have shown that every avoided hospitalization due to palivizumab results in $10,000 to $50,000 saved, depending on the country and adjusting for direct and indirect costs[22,28]. The broader use of long-acting antibodies like nirsevimab, which offers season-long protection, is expected to amplify these financial benefits. Similarly, decreased parental absenteeism from work and the reduced need for high-cost caregiving results in less financial strain for the affected families[29,30].

Conclusions

Implementation of mAbs for RSV-associated infections has shown clear clinical and financial benefits in abundant pieces of evidence. As shown in available data, mAbs lead to a significantly lower rate of severe RSV infections when comparing with control groups, highlighting its high effectiveness. Clinically, this translated to fewer hospitalizations, ICU admissions, need for mechanical ventilation, and significantly better patient outcomes. On the other hand, fewer severe cases lead to significant cost savings for both the public health and familiar systems, easing the economic burden on both ends. Overall, mAbs offer a powerful preventive strategy, protecting vulnerable children and providing great clinical and financial benefits.

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