Anales de Pediatría 99 (2023) 257–263

analesdepediatría

www.analesdepediatria.org

SPECIAL ARTICLE

Nirsevimab for the prevention of respiratory syncytial virus disease in children. Statement of the Spanish Society of Paediatric Infectious Disease (SEIP)

Laura Francisco[a], Marta Cruz-Cañete[b], Carlos Pérez[c], José Antonio Couceiro[d], Enrique Otheo[e], Cristian Launes[f], Carlos Rodrigo[g], Ana Belén Jiménez[h], Marta Llorente[i], Abián Montesdeoca[j], José Rumbao[k], Cristina Calvo[l], Susana Frago[m], Alfredo Tagarro[n,*]

[a] *Centro de Salud San Fermin, Gerencia Asistencial de Atención Primaria, Dirección Asistencial Centro, Madrid, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[b] *Servicio de Pediatría, Hospital de Montilla, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[c] *Servicio de Pediatría, Hospital Universitario de Cabueñes, Gijón, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[d] *Servicio de Pediatría, Complejo Hospitalario de Pontevedra, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[e] *Servicio de Pediatría, Hospital Universitario Ramón y Cajal, Madrid, Universidad de Alcalá. Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[f] *Servicio de Pediatría, Hospital Sant Joan de Déu (HSJD), Barcelona, Spain, Universidad de Barcelona, Barcelona, Spain, Grupo de Investigación en Enfermedades Infecciosas Pediátricas, Institut de Recerca Sant Joan de Déu, Barcelona, Spain, CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, España. Departamento de Cirugía y Especialidades Médico-Quirúrgicas, Facultad de Medicina y Ciencias de la Salud, Universitat de Barcelona, Barcelona, Spain, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[g] *Servicio de Pediatría, Hospital Universitari Germans Trias i Pujol, Barcelona, Facultad de Medicina-Unidad Docente Germans Trias i Pujol, Universidad Autónoma de Barcelona, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[h] *Servicio de Pediatría, Fundación Jiménez Díaz, Madrid, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[i] *Servicio de Pediatría, Hospital de Arganda, Madrid, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[j] *Atención Primaria, Centro de Salud de Guanarteme, Las Palmas de Gran Canaria, Miembro del CAV-AEP, Spain*
[k] *Servicio de Pediatría, Hospital Reina Sofía, Córdoba, Spain*

DOI of original article: https://doi.org/10.1016/j.anpedi.2023.09.006
* Corresponding author.
E-mail address: alfredotagarro@gmail.com (A. Tagarro).

[l] *Servicio de Pediatría, Enfermedades Infecciosas y Tropicales Pediátricas, Hospital Universitario la Paz, Fundación IdiPaz, CIBERINFEC ISCIII, Madrid, Spain, Universidad Autónoma de Madrid, Red de Investigación Traslacional en Infectología Pediátrica (RITIP), Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*
[m] *Representante de Familias de Pacientes, Miembro de la Asociación de Padres de Niños Prematuros (APREM), Spain*
[n] *Servicio de Pediatría, Hospital Universitario Infanta Sofía, Fundación Para la Investigación Biomédica e Innovación Hospital Universitario Infanta Sofía y Hospital del Henares (FIIB HUIS HHEN). Instituto de Investigación 12 de Octubre (imas12), Madrid, Universidad Europea de Madrid, Grupo de Trabajo de Infecciones Respiratorias de la Sociedad Española de Infectología Pediátrica, Spain*

Received 2 July 2023; accepted 7 September 2023
Available online 22 September 2023

KEYWORDS
Respiratory syncytial virus;
Nirsevimab;
Bronchiolitis;
Prevention;
Monoclonal antibody

Abstract:
Introduction: Nirsevimab, a monoclonal antibody for the prevention of disease caused by respiratory syncytial virus (RSV), has recently been approved for use in Europe and Spain.
Objectives: To provide recommendations for the administration of nirsevimab for prevention of RSV disease.
Methods: The approach chosen to develop these recommendations involved a critical review of the literature and the use of the Delphi and GRADE methods. An expert group was formed. The group engaged in three rounds to define the questions, express support or opposition, grade recommendations and establish the agreement or disagreement with the conclusions.
Results: In the general neonatal population, routine administration of nirsevimab is recommended to reduce the frequency of illness and hospitalisation for bronchiolitis and RSV lower respiratory tract infection. Nirsevimab is recommended for all infants born in high-incidence RSV season and infants aged less than 6 months at the season onset. In infants born preterm between 29 and 35 weeks of gestation, with haemodynamically significant heart disease or with chronic lung disease, routine administration of nirsevimab is recommended to reduce the incidence of disease and hospitalisation due to bronchiolitis and RSV lower respiratory tract infection. In patients in whom palivizumab is currently indicated, its substitution by nirsevimab is recommended to reduce the burden of bronchiolitis.
Conclusions: Routine administration of nirsevimab to all infants aged less than 6 months born during the RSV season or aged less than 6 months at the start of the winter season is recommended to reduce the burden of disease and the frequency of hospitalization due to bronchiolitis.

PALABRAS CLAVE
Virus respiratorio sincitial;
Nirsevimab;
Bronquiolitis;
Prevención;
Anticuerpo monoclonal

Nirsevimab para la prevención de la enfermedad por virus respiratorio sincitial en niños. Posicionamiento de la Sociedad Española de Infectología Pediátrica

Resumen
Introducción: Recientemente se ha aprobado en Europa y en España el uso de nirsevimab, un anticuerpo monoclonal para la prevención de la enfermedad por virus respiratorio sincitial (VRS).
Objetivos: Facilitar unas recomendaciones para la administración de nirsevimab para la prevención de la enfermedad por VRS.
Métodos: Para la elaboración de estas recomendaciones, se decidió realizar una revisión crítica de la literatura, utilizar la metodología Delphi y la metodología GRADE. Se definió un grupo de expertos. Se realizaron tres rondas para definir las preguntas, manifestarse a favor o en contra, graduar la recomendación, y definir el acuerdo o el desacuerdo con las conclusiones.
Resultados: En la población general de recién nacidos, se recomienda administrar rutinariamente nirsevimab para reducir la enfermedad y la hospitalización por bronquiolitis y enfermedad de vías bajas por VRS. Se recomienda administrar nirsevimab a todos los lactantes que nazcan en la estación de alta incidencia de VRS y aquellos que cuando ésta comience, tengan menos de 6 meses. En los pacientes prematuros de 29 a 35 semanas de edad gestacional,

en los lactantes con cardiopatía hemodinámicamente significativa y lactantes con enfermedad pulmonar crónica se recomienda rutinariamente administrar nirsevimab para reducir la enfermedad y la hospitalización por bronquiolitis y enfermedad de vías bajas por VRS. En los pacientes con indicación actual de palivizumab, se recomienda sustituir palivizumab por nirsevimab para reducir la carga de enfermedad de bronquiolitis.

Conclusiones: Se recomienda administrar rutinariamente nirsevimab a todos los recién nacidos menores de 6 meses nacidos en la estación de VRS o que tengan menos de 6 meses cuando entran en la estación invernal, para reducir la carga de enfermedad y la hospitalización por bronquiolitis.

Introduction

Respiratory syncytial virus (RSV) is one of the main causes of respiratory disease in children worldwide and the leading cause of hospitalization due to lower respiratory tract infection, including bronchiolitis and pneumonia. It is one of the leading causes of death in infants and children overall, and particularly in preterm infants. Most children are infected by RSV before age 2 years and up to 14% require medical attention for this reason in the first year of life.[1] The incidence of RSV-associated hospitalization in Europe is of approximately 1.8%.[1,2] It is estimated that 3.2 million children require hospital-based treatment for RSV infection each year.[1] Globally, RSV causes 1 out of 28 deaths in infants aged 28 days to 6 months, and 3 out of 4 related hospital admissions occur in previously healthy infants.[3] Since most deaths due to RSV occur in low-income countries that may not be included in hospital-based surveillance, the actual figures may be even worse. [4,5] Respiratory syncytial virus has been associated with recurrent wheezing in the long term, impaired lung function and increased use of health care resources.[6]

Effective strategies for RSV prevention are consequently of utmost importance to address this significant public health problem.[3,7–13] Vaccination programmes against the virus can reduce the incidence of RSV significantly.[3]

Until recently, the only preventive measure that was commercially available was a monoclonal antibody (MAb) against RSV, palivizumab, administered monthly to patients in whom it is indicated: infants born preterm or with chronic disease, usually haemodynamically significant heart disease and chronic respiratory disease.[14,15] Recently, Europe and Spain have authorised the use of nirsevimab, a monoclonal antibody, for prevention of RSV infection in infants aged less than 1 year, and several clinical trials that analysed the outcomes of its use in preterm infants born between 29 and 35 weeks of gestation, late preterm infants and term infants have also been published.[16–19]

Other tools are at the late phase of development, such as the prefusion F protein vaccine for pregnant women, which has recently been found efficacious in reducing the risk of hospital admission due to lower respiratory tract infection in the first 180 days of life, clesrovimab and other vaccines that are at different phases in the development process.[6,20]

Given these novelties in prevention and their potential relevance, the Sociedad Española de Infectología Pediátrica (SEIP, Spanish Society of Paediatric Infectious Diseases) considered that it would be relevant to issue an official position statement including recommendations on the use of nirsevimab for prevention of RSV infection through the Working Group (WG) on Respiratory Infections.

Objective

To provide recommendations for the use of nirsevimab for prevention of RSV-related disease in the paediatric population based on the currently available evidence applicable to our country.

Methods

The approach chosen to develop the recommendations was a critical literature review, the Delphi methodology and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method.

Based on the scientific evidence of highest quality (clinical trials and meta-analysis) published in the past 5 years, a series of questions was formulated.

The issue at hand was defined as ''issuing recommendations for the use of nirsevimab in children''. A panel of experts was appointed, which corresponded to the WG on Respiratory Infections of the SEIP. The members who had conflicts of interest were allowed to express their opinions in the process, but not allowed to vote.

External experts were also invited to join the panel: a member of the Advisory Committee on Vaccines of the Spanish Society of Pediatrics, an expert in health care administration and a patient representative, the latter for the purpose of including the preferences of the families of patients. The fact that bronchiolitis is an acute disease is one of the main reasons for the lack of patient associations specifically focused on this disease, so the group included a representative of the families of preterm infants.

Three facilitators were appointed: the coordinator, the secretary and a member of the WG of Respiratory Infections of the SEIP to develop the questionnaires, define the questionnaire rounds and structure the information. The facilitators carried out a literature review, searching the

Cochrane, Embase and PubMed databases for articles published in the last 5 years focused on the variables of interest and limited to research of the highest quality. The quality of the research was determined based on the study design: meta-analyses and clinical trials were given an a priori grading of ''high'' quality and observational studies an a priori grading of ''low'', subsequently upgrading or downgrading the initial ranking as applicable based on factors that increased or decreased the quality of the evidence. The search was specifically focused on clinical trials and meta-analyses. The facilitators forwarded the studies of highest quality, along with a summary of their main findings, to the rest of the group. The overall findings were summarised in a document distributed to all the experts. The studies were graded as being of high, moderate, low and very low quality based on the limitations, inconsistencies and directness or indirectness of the evidence.

The panel defined the variables of interest through questions. A first round was conducted to develop possible questions and identify the most relevant variables.

Then, questions were formulated starting from the variables of interest applying the Population, Intervention, Comparison and Outcome (PICO) framework. The members of the WG and invited experts rated the relevance of the variables on a scale from 1 to 9.

Variables with ratings of 6 or greater were categorised as ''very important variables'' (6 points) or ''key variables (7–9 points) and were selected for evaluation by the panel.

A second round involving all the members of the WG was devoted to defining their answers to the formulated questions in the form of statements (in favour/against) after discussing their opinions, and to grading the resulting recommendations (strong/weak) based on the degree of certainty that the benefits and advantages exceed the risks and drawbacks. We recommended reserving the rating as a strong recommendation for statements supported by meta-analysis results (as opposed to evidence from clinical trials alone) and in the absence of evidence of significant risks of costs. For instance, in the case of interventions supported by evidence from clinical trials but that have a high cost, associated with frequent or severe adverse effects or for which there is uncertainty regarding economic aspects or patient preferences, the strength of the recommendation should be weak, whereas for those supported by evidence from meta-analyses, with few adverse events, a low cost and easy to implement, the recommendation should be strong.[21]

A third round was devoted to establishing the agreement or disagreement with the conclusions from the second round by means of a Likert scale ranging from 1 to 5 points.[22]

At least 70% of the panel had to agree with the recommendation for it to be accepted as such. If 70% of the experts expressed ''agreement'' or ''strong agreement'' with the recommendation, the item was considered acceptable. If 70% of the experts expressed ''disagreement'' or ''strong disagreement'', it was considered sufficient justification to eliminate the item. The remaining items had to be re-evaluated in the next round.

A remote meeting was held to finish the discussion and define the key points. The panel drafted the recommendations (in favour/against). Each recommendation was then graded (strong/weak). The final recommendations were established taking into account the quality of the evidence, the risk of bias, the risk-benefit ratio, economic variables and other aspects that emerged during the discussion.

Results

Recommendation 1: In the population of healthy term and late preterm infants, routine administration of nirsevimab is recommended to reduce the incidence of hospitalization due to RSV-associated lower respiratory tract infection and bronchiolitis (in favour, weak recommendation).

Rationale:

Nirsevimab has been found to decrease the incidence of hospitalization due to RSV in term and late preterm infants with a high level of certainty. Significant adverse effects have not been reported in association with the administration of nirsevimab.[17,18]

The recommendation is weak because there have been no other studies reproducing the findings of the trials conducted by the pharmaceutical industry, and therefore there are also no meta-analyses including evidence from additional trials. There are additional uncertainties, chiefly regarding its implementation, cost, acceptance by families, safety after post-authorization large-scale commercialization or the evolution of the virus toward potential forms of drug resistance.

Recommendation 2: In the general population of term and late preterm infants, routine administration of nirsevimab is recommended to reduce the incidence of RSV-associated lower respiratory tract infection and bronchiolitis (in favour, weak recommendation).

Rationale:

Nirsevimab has been found to reduce the incidence of medically-attended RSV infection in term and late preterm infants. Significant adverse effects have not been reported in association with the administration of nirsevimab.[17,18]

The recommendation is weak because there have been no other studies reproducing the findings of the trials conducted by the pharmaceutical industry, and therefore there are also no meta-analyses including evidence from additional trials. There are additional uncertainties, chiefly regarding its implementation, cost, acceptance by families, safety after post-authorization large-scale commercialization or the evolution of the virus toward potential forms of drug resistance.

Recommendation 3: Administration of nirsevimab is recommended for all neonates born during the RSV season and infants aged less than 6 months at the season onset (in favour, strong recommendation).

Rationale:

As noted above, clinical trials found that nirsevimab achieved a reduction in the incidence of medically-attended RSV infection, hospitalization and severe disease due to RSV (efficacy of 78%; 95% confidence interval [CI], 49%–91%). Infants aged less than 6 months are most vulnerable and most likely to require hospitalization and intensive care, and therefore it is reasonable to assume that the risk-benefit ratio is more favourable in this age group, so the panel is in favour of issuing a strong recommendation for the administration of nirsevimab in this population.[1,6,16–18,23,24]

Recommendation 4: In infants born preterm between 29 and 35 weeks of gestation, with haemodynamically signif-

icant heart disease or chronic pulmonary disease, routine administration of nirsevimab is recommended to reduce the incidence of hospitalization due to RSV-associated lower respiratory tract infection and bronchiolitis (in favour, strong recommendation).

Rationale:

Nirsevimab has been found to reduce the frequency of hospital admission due to RSV in this subset of infants, who are at high risk. Significant adverse events have not been reported in association with the administration of nirsevimab.[16,19] This population is particularly vulnerable and more likely to require hospitalization and intensive care, and therefore it is reasonable to assume that the risk-benefit ratio is more favourable in this group, so the panel is in favour of issuing a strong recommendation for the administration of nirsevimab in this population.

Recommendation 5: In infants born preterm between 29 and 35 weeks of gestation, with haemodynamically significant heart disease or chronic pulmonary disease, routine administration of nirsevimab is recommended to reduce the incidence of RSV-associated lower respiratory tract infection and bronchiolitis (in favour, strong recommendation).

Nirsevimab has been found to reduce the frequency of hospitalization due to RSV in this subset of infants, who are at high risk. Significant adverse events have not been reported in association with the administration of nirsevimab.[16,19]

This population is particularly vulnerable and more likely to require hospitalization and intensive care, and therefore it is reasonable to assume that the risk-benefit ratio is more favourable in this group, so the panel is in favour of issuing a strong recommendation for the administration of nirsevimab in this population.

Recommendation 6: In patients in whom palivizumab is currently indicated, the substitution of nirsevimab for palivizumab is recommended to reduce the burden of RSV-associated bronchiolitis (in favour, weak recommendation).

Rationale:

In infants in whom administration of palivizumab is indicated (born preterm between 29 and 35 weeks of gestation, with haemodynamically significant congenital heart disease or with chronic pulmonary disease), nirsevimab has proven efficacious, with adverse events comparable to those of palivizumab (high certainty).[25] The incidence of medically-attended disease was similar (nirsevimab, 0.6% vs palivizumab, 1.0%), although the clinical trial that compared the safety of these two agents did not report risk or *P* values. A recent meta-analysis found a greater reduction in the rate of RSV infection per 1000 participants with nirsevimab compared to palivizumab (nirsevimab, −123 cases [95% CI, −138 to −100] vs palivizumab, −108 cases [95% CI, −127 to −82]) as well as in the rate of RSV-associated hospitalization per 1000 participants (nirsevimab, −54 [95% CI, −64 to −38] vs palivizumab, −39 (95% CI, −48 to −28).[8]

Recommendation 7: Infants entering their first RSV season, including those aged 6 months to 1 year at the onset of the season (and who have not received it previously), may be given nirsevimab, although the panel does not offer a specific recommendation.

Rationale:

Nirsevimab has been found to decrease the incidence of RSV-associated disease and hospitalization in term and late preterm newborns who received immunoprophylaxis in the first year of life.[17,18] Although most of the panel agreed, the 70% threshold established to define consensus was not reached. None of the panel members expressed disagreement, but more than 30% neither agreed nor disagreed.

Discussion

The panel recommends universal prophylaxis against RSV in term infants and preterm infants born between 29 and 35 weeks of gestation to reduce the incidence of RSV-associated medically attended lower respiratory tract infection and hospitalization with an intervention currently available, nirsevimab. A preliminary analysis of data from the MELODY trial (a randomised controlled trial comparing nirsevimab to placebo in term and late preterm infants) evinced a reduction in medically-attended RSV-associated lower respiratory tract infection RSV at 150 days of 74.5% (IC 95%, 49–87), but did not find a statistically significant decrease in the rate of hospitalization.[17] However, once the trial completed enrolment with 3000 participants, the decrease became statistically significant.[18] Hospitalization decreased by 76% (95% CI, 49%–89%) and the incidence of severe medically attended infection (requiring oxygen and/or intravenous fluids) by 78.6% (95% CI, 48.8%–91%). Although at the time of this writing its results have yet to be published in a peer-reviewed journal, the HARMONIE trial, presented in May 2023 at the 41 st Annual Meeting of the European Society for Paediatric Infectious Diseases, seems to have found ample evidence of these benefits. The trial, conducted in the 2022–2023 RSV season under conditions similar to those in which nirsevimab would be used in real-world practice, included 8058 infants up to age 12 months (4037 received nirsevimab and 4021 the standard of care), and found benefits similar to those of the previously published trials, with a number needed to immunize (NNI) of 82 to prevent one hospitalization and of 285 to prevent hospitalization combined with severe disease.

The panel particularly recommends administration to infants born during the RSV season or aged less than 6 months at its onset, as well as high-risk groups (born preterm at 29–35 weeks, with haemodynamically significant heart disease or with chronic pulmonary disease).

To further qualify these recommendations, in particular in regard to some being weak despite the existence of well-designed and randomised trials that support them, we ought to highlight that there are some sources of uncertainty. First, additional trials have not been conducted to reproduce the findings of industry trials, and therefore there are no meta-analyses including the findings of other studies. Other important aspects that remain uncertain concern the implementation, cost and acceptance by families, post-marketing safety once nirsevimab is produced on a large scale or the potential development of resistance by the virus. Although previous trials and observational data suggest that the probability of the development of resistance to palivizumab is low,[26] emerging evidence on the evasion of mAbs by HIV and SARS-CoV-2 warrants caution. There is also a degree of uncertainty regarding the effectiveness and efficiency of the drug in populations in which it has not been studied, such as medium- and low-income regions. In

Spain, official recommendations and directives on how to approach the introduction of this monoclonal antibody are already available. The Ministry of Health recently published its recommendations for the use of nirsevimab for protection against RSV for the 2023–2024 season (working group on the use of nirsevimab against RSV infection of the Vaccination Planning and Registration Subcommittee of the Public Health Care Committee of the Interterritorial Council of the National Health Care System, Ministry of Health of Spain, July 2023). They are presented in a document developed by a working group specifically formed by the Subcommittee for this particular purpose, with the involvement of the Subcommittee itself, and professionals with expertise in paediatric care and paediatric infectious diseases, microbiology, neonatology and paediatric nursing. It carried out a policy evaluation and issued specific recommendations, ordered by level of priority, and only for the 2023–2024 season, for the following groups in the population: (1) Paediatric population at high risk of developing severe RSV-associated disease; and (2) Infants aged less than 6 months at the onset of or during the RSV season), despite there not being sufficient information to meet all the criteria required to support any modification to the immunization schedule of Spain, such as cost-effectiveness studies. The Sociedad Española de Neonatología (Spanish Society of Neonatology) has also issued a statement recommending the use of nirsevimab in all newborns and infants aged less than 6 months at the beginning of the RSV season, with repeated administration in the second season in infants with bronchopulmonary dysplasia or with risk factors for severe RSV infection, even if they are older than 6 months.[27]

On the other hand, it is important to take into account the upcoming authorization of competing products, such as the prefusion F vaccine for pregnant women,[20] which could work better in real-world practice in some health care systems. We must keep abreast of emerging evidence from potential head-to-head trials and the actual implementation of both strategies to assess which will be most suitable in the real world based on the characteristics of the area where they are implemented. The Joint Committee on Vaccination and Immunisation of the United Kingdom recommends the implementation of either strategy, as long as it is universal.[28] Lastly, new candidates, such as clesrovimab, are likely to be authorised in upcoming years. All these considerations, along with the lack of meta-analyses, led to the weak versus strong recommendation for some of the items.

Although recommendations 1 and 2 (in favour) are weak, recommendation 3 (in favour) is strong because it focuses not only on the indication but also the timing for use of nirsevimab. The panel unanimously agreed that the optimal window to protect infants is the first 6 months post birth, although this is not to say prophylaxis cannot be given between ages 6 to 12 months. Although the trials showed that nirsevimab offered greater protection to older infants with greater weights, it is the youngest infants that are most at risk of developing severe disease, so infants aged 6 months or less during the RSV season seem to be the best candidates for prophylaxis. Notwithstanding, the epidemiology of RSV may change, as illustrated by the COVID-19 pandemic, and it may not always be easy to identify the onset of the RSV season.

In infants born preterm between 29 and 35 weeks of gestation, infants with haemodynamically significant heart disease or chronic pulmonary disease, nirsevimab has been found to reduce the incidence of medically-attended lower respiratory tract infection by 70% (95% CI, 52.3%–81.2%; $P < .001$) and the incidence of hospitalization by 78.4% (95% CI, 51.9%–90.3%; $P < .001$).[16] However, it must be taken into account that efficacy studies did not include participants born before 29 weeks of gestation. In this subset, there is no evidence of the superiority of either drug. One study analysed the dosage of nirsevimab in infants born before 29 weeks through the extrapolation of pharmacokinetic data from the phase II and III MEDLEY safety trial.[19] The authors estimated the incidence of medically attended lower respiratory tract infection by extrapolating serum concentrations (areas under the concentration-time curve [AUCs]), and for extrapolation to be considered successful, more than 80% of infants in MEDLEY had to achieve serum nirsevimab exposures at or above the predicted efficacious target. The AUCs were above the target for the overall MEDLEY trial population (94%) and all subgroups of special interest: infants with chronic pulmonary disease (94%), infants with haemodynamically significant congenital heart defects (80%) and preterm infants delivered before 29 weeks of gestation (94%).

In newborns in whom palivizumab is indicated, administration of nirsevimab in its stead is warranted given the comparable risks and benefits,[25] the lesser economic cost and time involved for the health care system and the family and the administration of a single dose instead of 5.

Some experts in the panel consider that it is fair to expect that its efficacy will be similar in all patients with an indication of palivizumab, at a more affordable price and with the convenience of requiring the administration of only one dose. The same rationale would apply to the second RVS season in patients eligible for prophylaxis.

Conclusion

Routine administration of nirsevimab to all infants born during the RSV season or aged less than 6 months at the start of the winter season is recommended to reduce the burden of disease and the rate of hospitalization due to bronchiolitis.

Conflicts of interest

Cristina Calvo has engaged in scientific collaborations with Astra Zeneca and Sanofi.

References

1. Weinberg GA. Respiratory syncytial virus mortality among young children. Lancet Glob Health. 2017;5:e951–2.
2. Wildenbeest JG, Billard MN, Zuurbier RP, Korsten K, Langedijk AC, van deVen PM, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. Lancet Respir Med. 2023;11:341–53.
3. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399:2047–64.

4. Brady MT, Byington CL, Davies HD, Edwards KM, Jackson MA, et al. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:e620–38.
5. Hall AJ. 239 - Caliciviruses A2 - Long, Sarah S. In: Prober CG, Fischer M, editors. Principles and Practice of Pediatric Infectious Diseases (Fifth Edition) [Internet]. Elsevier; 2018. p. 1221–400. Available from: https://www.sciencedirect.com/science/article/pii/B9780323401814002395
6. Mazur NI, Terstappen J, Baral R, Bardají A, Beutels P, Buchholz UJ, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. Lancet Infect Dis. 2023;23:e2–21.
7. Prescott WA, Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. Pharmacoeconomics. 2010;28:279–93.
8. Sun M, Lai H, Na F, Li S, Qiu X, Tian J, et al. Monoclonal antibody for the prevention of respiratory syncytial virus in infants and children: a systematic review and network meta-analysis. JAMA Netw Open. 2023;6:e230023.
9. Li X, Bilcke J, Vázquez Fernández L, Bont L, Willem L, Wisløff T, et al. Cost-effectiveness of respiratory syncytial virus disease prevention strategies: maternal vaccine versus seasonal or year-round monoclonal antibody program in Norwegian children. J Infect Dis. 2022;226:S95–101.
10. Li X, Hodgson D, Flaig J, Kieffer A, Herring WL, Beyhaghi H, et al. Cost-effectiveness of respiratory syncytial virus preventive interventions in children: a model comparison study. Value Health. 2023;26:508–18.
11. Mahmud S, Baral R, Sanderson C, Pecenka C, Jit M, Li Y, et al. Cost-effectiveness of pharmaceutical strategies to prevent respiratory syncytial virus disease in young children: a decision-support model for use in low-income and middle-income countries. BMC Med. 2023;21:138.
12. Getaneh AM, Li X, Mao Z, Johannesen CK, Barbieri E, van Summeren J, et al. Cost-effectiveness of monoclonal antibody and maternal immunization against respiratory syncytial virus (RSV) in infants: evaluation for six European countries. Vaccine. 2023;41:1623–31.
13. Li X, Willem L, Antillon M, Bilcke J, Jit M, Beutels P. Health and economic burden of respiratory syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries. BMC Med. 2020;18:82.
14. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013 [citado 10 de abril de 2023]; Available from: https://doi.wiley.com/10.1002/14651858.CD006602.pub4
15. Garegnani L, Styrmisdóttir L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JV. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. Cochrane Acute Respiratory Infections Group, editor. Cochrane Database Syst Rev. 2021 [citado 10 de abril de 2023]. Available from: http://doi.wiley.com/10.1002/14651858.CD013757.pub2
16. Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020;383:415–25.
17. Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med. 2022;386:837–46.
18. Muller WJ, Madhi SA, Seoane Nuñez B, Baca Cots M, Bosheva M, Dagan R, et al. Nirsevimab for prevention of RSV in term and late-preterm infants. N Engl J Med. 2023:NEJMc2214773.
19. Simões EAF, Madhi SA, Muller WJ, Atanasova V, Bosheva M, Cabañas F, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health. 2023;7:180–9.
20. Kampmann B, Madhi SA, Munjal I, Simões EAF, Pahud BA, Llapur C, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med. 2023:NEJMoa2216480.
21. Goldet G, Howick J. Understanding GRADE: an introduction. J Evid Based Med. 2013;6:50–4.
22. Humphrey-Murto S, Varpio L, Gonsalves C, Wood TJ. Using consensus group methods such as Delphi and Nominal Group in medical education research. Med Teach. 2017;39:14–9.
23. Martinón-Torres F, Carmo M, Platero L, Drago G, López-Belmonte JL, Bangert M, et al. Clinical and economic burden of respiratory syncytial virus in Spanish children: the BARI study. BMC Infect Dis. 2022;22:759.
24. Martinón-Torres F, Carmo M, Platero L, Drago G, López-Belmonte JL, Bangert M, et al. Clinical and economic hospital burden of acute respiratory infection (BARI) due to respiratory syncytial virus in Spanish children, 2015–2018. BMC Infect Dis. 2023;23:385.
25. Domachowske J, Madhi SA, Simões EAF, Atanasova V, Cabañas F, Furuno K, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. N Engl J Med. 2022;386:892–4.
26. Wilkins D, Langedijk AC, Lebbink RJ, Morehouse C, Abram ME, Ahani B, et al. Nirsevimab binding-site conservation in respiratory syncytial virus fusion glycoprotein worldwide between 1956 and 2021: an analysis of observational study sequencing data. Lancet Infect Dis. 2023;23:856–66.
27. Statement of the Spanish Society of Neonatology, *Consulted*.
28. Respiratory syncytial virus (RSV) immunisation programme: Joint Committee on Vaccination and Immunisation (JCVI) advice, 7 June 2023. Consulted at https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-jcvi-advice-7-june-2023.