

Second-season Impact of Nirsevimab

Clinical Outcomes of RSV Disease in Patients Immunized During Their First Season

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Abstract: Nirsevimab provides passive immunization against respiratory syncytial virus, yet concerns exist regarding its long-term impact. This study analyzed respiratory syncytial virus-associated lower respiratory tract infection severity in hospitalized children immunized with nirsevimab more than 6 months prior. No significant differences were found compared with nonimmunized children. Findings suggest no increased risk in the following season, supporting nirsevimab's safety as a preventive strategy.

Key Words: respiratory syncytial virus, nirsevimab, immunization, antibody-dependent enhancement

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Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections in infants, often resulting in hospitalization and severe complications.¹ In recent years, nirsevimab, a monoclonal antibody designed for passive immunization, has emerged as a promising preventive measure against RSV in neonates and young infants.² Unlike traditional vaccines that stimu-

late an endogenous immune response, nirsevimab directly provides high-affinity antibodies targeting RSV.³

Clinical trials have demonstrated that nirsevimab confers protection against RSV for at least 6 months, aligning with the period of highest vulnerability in infancy.² However, since nirsevimab provides passive immunization rather than actively stimulating the immune system, it is believed not to induce a long-term immune memory response. Consequently, once antibody levels wane, infants may remain susceptible to RSV infection.³

A theoretical concern associated with passive immunization strategies is antibody-dependent enhancement (ADE), where subneutralizing antibody levels facilitate viral entry into host cells, potentially exacerbating disease severity.⁴ While ADE has been observed in some viral infections, evidence regarding the use of nirsevimab remains inconclusive. Some experts have raised concerns that as circulating nirsevimab levels decline, there may be an increased risk of severe RSV disease in subsequent exposures.³

Given these considerations, it is crucial to evaluate the long-term clinical outcomes of infants who received nirsevimab more than 6 months prior. This study aims to assess the severity of RSV-associated lower respiratory tract infections (RSV-LRTI) in hospitalized children who received nirsevimab more than 6 months prior and compare their clinical outcomes with those of nonimmunized patients in their first RSV season.

PATIENTS AND METHODS

This is a substudy of an ongoing multicenter prospective investigation of respiratory tract infections in children, funded by grants from the Spanish Health Research Fund, involving a tertiary and a secondary pediatric hospital in Madrid, Spain. The study was approved by the ethics committee of both hospitals. We included all patients between 6 and 24 months old admitted to the hospital for RSV-LRTI during 3 RSV seasons: (October 1, 2022–March 31, 2023), (October 1, 2023–March 31, 2024) and (October 1, 2024–February 28, 2025). In Spain, nirsevimab has been systematically administered to all infants under 6 months of age during the RSV season since October 2023, with immunization coverage ranging between 88% and 92% of newborns during the 2023–2024 season.⁵

RSV-LRTI was defined as signs of a viral upper respiratory infection, with breathing difficulties and one of the following examination findings: crackles, wheezing, or diminished vesicular murmur. Both centers followed the same standardized hospitalization criteria. We excluded infants who had received nirsevimab from 0 to 180 days before the onset of symptoms and those who had palivizumab immunization.

All patients were assessed by an attending physician. Clinical and epidemiological characteristics were collected. During hospitalization and as part of the study, a physician completed a research-specific questionnaire including the following variables:

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TABLE 1. Patients’ Demographic, Clinical and Laboratory Data

	Non-nirsevimab (n = 196)	Nirsevimab (n = 34)	P Values
Absolute Frequencies (%)			
Sex (male)	121 (62)	18 (53)	0.34
Prematurity or chronic diseases	21 (12)	1 (3)	0.14
Prior respiratory admission	36 (21)	4 (12)	0.34
Fever	152 (78)	28 (85)	0.49
Viral coinfection	52 (26)	6 (28)	0.62
Oxygen supplementation	179 (92)	33 (97)	0.48
High-flow oxygen	84 (43)	10 (29)	0.18
Noninvasive ventilation	17 (9)	0 (0)	0.08
ICU admission	18 (9)	1 (3)	0.32
Antibiotic therapy	91 (47)	1 (33)	0.18
Mean (SD)			
Leukocytes (/mm ³)	12291 (5607)	8679 (8019)	0.06
CRP value (mg/L)	36.0 (53.2)	38.2 (35.7)	0.74
Age (months)	12.6 (5)	13.3 (3.3)	0.45
Median (IQR)			
Fever duration (days)	3 (3)	3 (4)	0.35
Temperature (°C)	39.0 (0.8)	38.8 (0.7)	0.55
Length of hospitalization (days)	4 (3)	4 (3)	0.58
Oxygen support duration (days)	4 (3.5)	3 (3)	0.16
ICU stay length (days)	3 (2.25)	2 (0)	0.51

Non-nirsevimab: children not immunized with nirsevimab during their first RSV season. Nirsevimab: children who received nirsevimab more than 6 months prior. Data are presented as the median with the IQR in the parentheses, as the mean with the SD in the parentheses, or as absolute frequencies with the percentage in parentheses. CRP indicates C-reactive protein; ICU, intensive care unit.

sex, age, admission date, previous nirsevimab administration, history of prematurity and underlying chronic diseases, previous hospitalizations due to respiratory illness, fever, and maximum axillary temperature, virological study results, oxygen supplementation and ventilatory support required, intensive care unit (ICU) admission, length of hospitalization and duration of oxygen support, antibiotic therapy administration, total white blood cell count, and C-reactive protein (CRP) serum levels at admission.

Study Procedures

Nasopharyngeal aspirates were collected within 24 hours of admission. Respiratory virus detection was performed via real-time multiplex RT-PCR (SuperScript III Platinum One-Step Quantitative RT-PCR System, Invitrogen, Waltham, MA).

Data Analysis

The analysis compared 2 groups of hospitalized children with RSV-LRTI: those who had received nirsevimab more than 6 months before admission, and those who were nonimmunized during their first RSV season. Information was analyzed using the IBM SPSS Statistics version 26 software. Continuous variables were presented as means and standard deviations (SDs), or medians and interquartile ranges (IQRs). Categorical variables were expressed as frequencies and percentages. The normal distribution of groups was analyzed via the Kolmogorov–Smirnov test and homoscedasticity via Levene’s test. Associations among independent continuous variables between nirsevimab and non-nirsevimab groups were compared using Student’s *t*-test (or Mann–Whitney test when appropriate as a nonparametrical test). Categorical variables were statistically analyzed with the chi-square test (or Fisher’s exact test when the sample size was small). Statistical significance was defined as a level of *P*-value <0.05.

RESULTS

During the study period, a total of 1288 patients younger than 2 years old were admitted to the hospital for LRTI, of whom

236 met the inclusion criteria (between 6 months and 2 years old and hospitalized due to RSV-LRTI). Six patients were excluded for having received nirsevimab within the previous 6 months.

Among the 230 eligible patients, 61% (140/230) were male, with a mean age of 12 months (SD: 2.1). Fever was reported in 79% (180/230) of cases. Eighty-five percent (196/230) had not received nirsevimab, while 15% (34/230) had received it more than 6 months prior, with a mean interval of 10.8 months (SD: 4.3) since administration.

Regarding seasonal distribution, during season 1 (October 1, 2022–March 31, 2023), 117 patients were hospitalized with RSV-LRTI, none of whom had received nirsevimab. In season 2 (October 1, 2023–March 31, 2024), 54 patients were admitted with RSV-LRTI, and none had received nirsevimab either. In season 3 (October 1, 2024–February 28, 2025), 59 patients were hospitalized with RSV-LRTI, 34 of whom (58%) had previously received nirsevimab.

Table 1 compares the 2 groups (with and without nirsevimab). No significant differences were observed in patient age, sex, history of underlying conditions, previous hospitalizations due to respiratory illness, or prematurity. Similarly, no significant differences were found in the presence of fever, maximum recorded temperature, or coinfection with other viruses.

Regarding severity parameters, no statistically significant differences were observed between the groups concerning the need for oxygen therapy, which was required by 97% of patients in the nirsevimab group versus 92% in the nonimmunized group (*P* = 0.48), or the need for high-flow oxygen therapy, which was administered to 29% of patients in the nirsevimab group compared with 43% in the nonimmunized group (*P* = 0.18). No patient in the nirsevimab group required noninvasive ventilation during the second season following administration, whereas 9% of nonimmunized patients did. However, this difference did not reach statistical significance (*P* = 0.08). Admission to the ICU was necessary for 3% of patients in the nirsevimab group compared with 9% of nonimmunized patients (*P* = 0.32).

Furthermore, no differences were observed between the groups in terms of hospitalization duration, with a median length of stay of 3 days (IQR: 3) in the nirsevimab group versus 3.5 days (IQR: 4) in the nonimmunized group ($P = 0.58$).

Patients who had received nirsevimab in the previous season were not more likely to receive antibiotic therapy or exhibit higher levels of acute-phase reactants in blood analysis. Although the difference was not statistically significant ($P = 0.059$), the nonimmunized group showed a higher mean leukocyte count: 12,290 leukocytes/mm³ (SD: 5607) compared with previously immunized patients' 8679 leukocytes/mm³ (SD: 8019).

DISCUSSION

A potential ADE associated with nirsevimab has been hypothesized following the decline in neutralizing antibody titers, which could lead to increased disease severity during the second RSV season. However, according to our study, there is no increased risk of developing more severe disease in hospitalized patients 6–24 months of age with RSV-LRTI immunized against RSV more than 6 months prior.

To date, only 1 study has addressed this issue. Dagan et al⁶ analyzed hospitalized RSV-LRTI patients who had received nirsevimab or a placebo during their first RSV season and compared disease severity in their second RSV season, defined as day 362–511 post-nirsevimab or post-placebo. Their analysis included 22 patients who had been immunized with nirsevimab and 11 who had received a placebo. Like our findings, their study did not report significant differences in disease severity between the 2 groups.

Although our study includes a larger sample size, the limited number of patients remains a constraint that may have reduced the ability to detect differences between the 2 groups. However, our findings suggest that if any differences exist, rather than amplifying disease severity, immunization with nirsevimab may even confer a certain degree of residual protection, persisting for an average of 10.8 months after administration. The Melody study reports that anti-RSV neutralizing antibodies remain elevated for up to 12 months postadministration and suggests that since nirsevimab does not prevent infection, it does not inhibit the natural immune response to RSV infection.^{7–8}

Furthermore, although statistical significance was not reached, our results indicate that previously immunized patients may exhibit a lower inflammatory response to RSV infection, as

reflected in lower leukocyte counts compared with nonimmunized patients. This difference could reflect a modulation of the inflammatory response mediated by the presence of neutralizing antibodies and their interaction with Fcγ receptors, which play a key role in cellular responses to infection.³ This raises the question of whether prior immunization with nirsevimab could influence leukocyte recruitment or activation during subsequent RSV infections, potentially leading to a more controlled inflammatory response. Further studies are needed to clarify this potential immunomodulatory effect.

In conclusion, our study provides reassurance regarding the safety of nirsevimab during the second RSV season in previously immunized children. The absence of an increase in disease severity supports the feasibility of this passive immunization strategy as an effective tool for preventing severe RSV infections in early childhood.

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