OPINION OF THE SCIENTIFIC COUNCIL OF THE **NATIONAL COLLEGE OF TEACHING GENERALISTS**

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Nirsevimab (Beyfortus®) to prevent RSV respiratory infections

Infant bronchiolitis heals spontaneously in over 95% of cases, but 2-3% of children under one year of age, 87% of whom have no identified risk factors, are hospitalized for severe bronchiolitis[1]. On August 1st, 2023, the Commission de la transparence (CT)[2] granted nirsevimab (Beyfortus®) a moderate Medical Service Rendered (SMR) and a minor Improvement in Medical Service Rendered (ASMR) in the therapeutic strategy for "the prevention of lower respiratory tract infections due to RSV in newborns and infants with or without risk factors and not eligible for palivizumab, during their first season of RSV circulation". Since 1999, palivizumab (Synagis®) has been available for the same indication, but exclusively for infants at high risk of severe disease[3].

Beyfortus® and Synagis® are not vaccines, but monoclonal antibodies that prevent RSV infection through passive immunity for several months. The main practical difference between Beyfortus® *and* Synagis® is their ease of use (1 injection vs. ≥ 5).

The marketing authorization and reimbursement of Beyfortus® are based on the publication of 3 randomized trials designed and financed by the AstraZeneca® laboratory (sometimes in association with the Sanofi® laboratory), in which the laboratory was involved in analyzing the data and writing the articles and trial reports.

In infants at high risk of severe disease: Trial D5290C00003

This randomized, double-blind[4] *versus* placebo trial exclusively included infants at high risk of severe disease (healthy premature infants aged < 1 year). Randomization allocated 960 infants to the nirsevimab group and 484 to the control group. Within 150 days post-injection, there were 25 (2.6%) cases of symptomatic RSV lower respiratory infections (primary endpoint) in the nirsevimab group and 46 (9.5%) in the placebo group: $p < 0.001$, number needed to treat (NNT) = 15, and 8 (0.8%) hospitalizations for lower respiratory infection due to RSV in the treatment group and 20 (4.1%) in the placebo group (hierarchical secondary endpoint): $p < 0.001$, NNT = 31. There was no difference in overall tolerability or severe adverse events between the 2 groups. These results are significant only for the population of infants at high risk of severe forms.

In healthy infants: MELODY trial

This randomized, double-blind, placebo-controlled Phase III trial[5] measured the efficacy and safety of Beyfortus® in healthy infants during their first RSV bronchiolitis epidemic season. Within 150 days of injection, there were 12 (1.2%) RSV lower respiratory infections requiring medical consultation (primary endpoint) in the nirsevimab group and 25 in the control group (5%): $p < 0.001$, NNT = 27.

The efficacy of Beyfortus® on RSV lower respiratory infections requiring consultation in low-risk infants has been well demonstrated. However, the efficacy of Beyfortus® on hospitalizations in this population has not been proven, as the results must be interpreted with caution. In fact, the protocol was amended to pool the results with a second cohort (designed exclusively to increase the number of participants in order to identify the rarest adverse events), in order to obtain a sufficient sample size to reach a conclusion on this criterion[5]. In the 2 cohorts of this trial, hospitalizations were an exploratory endpoint.

Tolerance study in infants at high risk of severe disease: MEDLEY trial

This randomized, double-blind trial[6] compared the tolerability of nirsevimab with that of palivizumab (primary objective). The authors included infants aged ≤ 1 year at high risk of severe form (pre-mature and or with congenital heart disease with hemodynamic impairment or severe chronic respiratory pathology). The incidence of adverse events was similar between the 2 groups.

Comments

In the light of published scientific data, the CNGE Scientific Advisory Board notes that Beyfortus® is effective against RSV infections, but that this efficacy has not been demonstrated (to date) in reducing hospitalizations in the general population of low-risk infants[6]. A shared decision-making process with parents should be based on a decision-making tool designed by caregivers and parents, and based on valid scientific data.

The results of the "real-life" HARMONIE randomized trial are due to be published in February 2024. These results are eagerly awaited, but the absence of a blinding procedure greatly attenuates the trial's level of proof.

It is essential that any therapy intended for the general population should benefit from a medico-economic evaluation and be rigorously and scientifically assessed in the population in which it is indicated. The SC will be attentive to "real-life" studies in order to :

– evaluate the impact of this drug on hospitalizations of low-risk infants;
– evaluate adverse effects on a large population;
– measure the cost-effectiveness of this treatment;
– monitor the appearance of any RSV mutations (CNR data).

The measures recommended by the HAS[8] - barrier measures, symptomatic medications, upper airway clearance, pulse oximetry monitoring, food fractionation and adequate caloric intake - are tried-and-tested measures that should be continued in the management of infant bronchiolitis (physiotherapy not recommended[8]).

References

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