EDITORIAL

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Nirsevimab brings breakthrough in the prevention of respiratory syncytial virus infection in infants – Importance of design

Ground-breaking advances have occurred during the recent few years in the prevention and treatment of respiratory syncytial virus (RSV) infection, which signifies the end of failures in the previous up to six decades of attempts to create or discover effective and safe approaches for prevention and treatment of RSV, esp. severe and life-threatening RSV infections in infants and young children. Studies on prevention with nirsevimab,[1–4] prevention with a new vaccine (RSVpreF vaccine),[5–9] and treatment with EDP-938[10–12] have obtained exciting results and evidence which are promising and encouraging to let people be crowing with delight for the arrival of the new era of fights against RSV! In this brief commentary, we review the clinical studies on nirsevimab and try to learn what roles the design has played in the studies.

Nirsevimab is a recombinant human monoclonal antibody. It can bind to F1 and F2 subunits of RSV fusion protein at a highly conserved epitope and it locks the fusion protein in the prefusion conformation to block viral entry into the host cell (bronchial epithelial cells). This monoclonal antibody has greater potency at inhibiting RSV than palivizumab in cell culture and animal models.[2] After its successful clinical trial reported in 2020,[1] in a further clinical trial, it was further demonstrated to be very effective and safe in the prevention of medically attended RSV-associated lower respiratory tract infection (LRTI) in preterm and term infants, healthy or those having underlying heart or lung disorders.[2]

MAJOR EVIDENCE FOR EFFICACY AND SAFETY OF NIRSEVIMAB

Randomized placebo-controlled blinded clinical trials for efficacy and safety of nirsevimab in the prevention of medically attended acute LRTI with RSV in premature and term infants[1,2] and a pooled analysis[4] of data from three clinical trials including the aforementioned two, all demonstrated that the drug was effective and safe. The major evidence included the following. The primary endpoints in the three reports were the same: medically attended acute LRTI caused by RSV in either subgroup A or B, which were significantly lower in the nirsevimab group than in the placebo group ($P < 0.001$), and the efficacy was 71.1%–79.5%; although a secondary efficacy endpoint in the study of Hammitt et al.,[2] the rates of hospitalization for RSV-associated LRTI could not reach the significance level, results of a prespecified pooled analyses showed the efficacy of 77.3% and significantly lower hospital admission rate for LRTI (1% *vs*. 3%, $P = 0.0002$) in the analyses of Simões et al.[4] Subgroup analyses showed that the efficacy of nirsevimab was consistent across all subgroups and degrees of disease severity. The number of cases and hospitalization for RSV-LRTI averted per 1000 cases treated was up to 75.0 and 16.0; the number of cases needed to treat for averting one case of RSV-LRTI or hospitalization was 14 and 62, respectively.

Pharmacokinetic data showed that the level of the effective drug concentration could persist for a whole RSV season (approximately 5 months) in the participants' sera. Antidrug antibody was found to exist in the serum of 6.1% of participants in the nirsevimab group but tended to develop later and did not affect the pharmacokinetics of the drug over the RSV season. Serious adverse events occurred in 6.8% of nirsevimab and 7.3% of placebo group infants. The safety of nirsevimab was well accepted.

Because of the evidence mentioned above, nirsevimab was approved by the European Medicines Agency by the end of October 2022 and by the UK on November 7, 2022.[13,14]

THE DESIGN OF THE PRODUCT

The exciting successes of the clinical trials on nirsevimab for the prevention of RSV infection in infants must have

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been supported and facilitated by many different factors, and the design of the product itself as well as that of the clinical trials must have played extremely important roles. Novelty in the design of the product may include the following aspects.

1. Change of strategy against RSV infection from treatment to prevention is an important transition. After a disease esp. a life-threatening disease already occurs, even though effective therapies do exist, management of the patient is always passive, and may not always succeed. It is well-accepted that prevention is the most radical strategy for a disease.
2. The fusion protein of RSV was chosen as the target of the monoclonal antibody nirsevimab because this protein is a necessary component for the virus to enter the host cells; furthermore, nirsevimab binds to a highly conserved epitope of this protein that may have a very low possibility of escaping from the effect of the antibody by variation of its gene.[13,14]
3. The Fc segment of the nirsevimab molecule was specially designed (by modifying with a triple amino acid substitution) to prolong its serum half-life to ensure the final product would be able to cover a whole RSV season of 5 months after injection.[14]
4. On the other hand, the molecular design also increased the binding activity of the antibody to the antigen significantly, which was demonstrated to be over 50-fold higher than that of palivizumab *in vitro* and up to 9-fold greater *in vivo*.[14]
5. The antibody molecule was designed and engineered to be able to bind to both subgroups A and B of RSV, this is important since both subtypes circulate in different regions and seasons.

DESIGN OF THE CLINICAL TRIALS

The clinical trials for the prevention of RSV infections with nirsevimab in healthy preterm and term infants formed an excellent paradigm in terms of design in the following aspects.

1. The participant populations chosen by the investigators were healthy preterm and term infants, who were also susceptible to RSV infection and therefore also need to be protected, otherwise a much larger population would be exposed to the risk of being infected with RSV.
2. The investigators especially considered that infants eligible in both the north and south hemispheres should be enrolled to see if the efficacy and safety of nirsevimab are the same or similar between the two hemispheres. Many previous clinical trials for respiratory infections did not consider this issue.
3. Stratification of the participants into subgroups according to certain important factors such as age, sex, race or ethnicity, gestational age, etc. was performed in the two clinical trials, which is very important to elucidate if the product is generally effective and safe, and which is also associated with the generalized application of the product. An important factor that should always be kept in mind for design is the presence or absence of some severe underlying disorders, such as congenital heart disease or bronchopulmonary dysplasia.
4. The studies included pharmacokinetic investigations, which provide important data on the persistence of effective serum concentration and serum half-life of the drug, etc.
5. Antidrug antibody was detected in both studies, which may answer the questions like how often the antidrug antibody was detected in both groups of participants. Does the existence of the antibody affect the efficacy or safety of the drug? Does it reduce the serum concentration of nirsevimab?
6. The doses of intervention with pharmacotherapies are always an important part of the design of a clinical study, and in terms of multiple-dose intervention, the length of the treatment course is also an important issue. In the trial reported by Griffin et al.,[1] 50 mg nirsevimab was given to each infant in the nirsevimab group regardless of age or weight; although the difference in age was small, the body weight varied considerably (4.6 ± 1.9, range 2.7–6.5 kg). With this wider difference, two dosing regimens (50 mg nirsevimab for infants weighing <5 kg of body weight, and 100 mg for those ≥ 5 kg) were applied in the study by Hammitt et al.,[2] which was more reasonable.

The rigorous design of the product nirsevimab, and of the clinical trials must have been the cornerstones of the success of preventing LRTI in premature and term healthy infants and those having certain underlying severe heart or lung diseases.

Many of the clinical trial reports mention limitations. Applying a fixed dose of 50 mg nirsevimab to each infant regardless of body weight could have been a limitation, but this was corrected in the trial of Hammitt et al.[2] On the other hand, the trial of Griffin et al.[1] seems not to be double-blind. It is believed that double-blinded studies have better persuasiveness. The study design of Hammitt et al.[2] showed some superiority in dosage, blinding, and description of the findings such as the number of cases needed to treat to avert one case of RSV-LRTI, the number of cases averted per 1000 participants treated, and double blinding.

As seen in some other clinical trials of young infants, deaths may occur, and the causes of death are very difficult to determine. In the nirsevimab trials, out of the total

of 1943 infants in the two trials, eight deaths occurred; five in the 1963 cases who received nirsevimab and three in the 980 cases who received placebo. Hammitt et al.[2] pointed out that none of the serious adverse events, including the deaths, were considered by the investigators to be related to nirsevimab or placebo. The clinical investigators may need to explore how to modify and improve the design of clinical trials so that in case deaths occur among the participants, the causes of death could be confirmed easily. Providing additional recommendations to the parents for medical attendance and necessary clinical and laboratory examinations may help.

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CONFLICT OF INTEREST

Getu Zhaori is the editor-in-chief of *Pediatric Investigation*.

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