EDITORIAL

The future of RSV prevention is behind the door: immunization or antibodies?

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Respiratory syncytial virus (RSV) was first isolated in 1956 from a chimpanzee with a cold. It has a single RNA chain with negative polarity with 10 genes that encode for 11 proteins, 3 of whom are structural. According to the variability of the G protein there are two groups A and B. 12 different genotypes belong to Group A and 20 to Group B (1). It is ubiquitous and 50% of the infants are infected during the first year of life and more than 70% at the end of the second year (2).
The most important structural protein of RSV is the F protein. F protein has two conformations pre-F and post-F. The pre-F protein has 5 known epitopes and only two of them remain on post-F. Antibodies against post-F epitopes are less neutralizing than antibodies against pre-F epitopes. The conformation pre-F is more stable comparing to the post -F and probably this can be a strategy of the virus to escape neutralizing antibodies (3). Antibodies induced by vaccines and monoclonal antibodies against antigens of pre-F protein sites have a higher neutralizing activity. RSV can affect all the age and normally it can cause a more severe disease in the extremities of life, neonates, and elderly adulthood (3). A recent systematic review has shown that RSV cause more than 33.8 million RSV LRTI worldwide (22% of all LRTI are due to RSV), 3.4 million LRTI episodes requiring hospitalization and 199.000 deaths (99% in low-income countries) (4). A study performed in UK in the adult population has shown that RSV LRTI are the cause of more than 500,000 GP consultation (36% in adults >65 years), 18,000 hospitalizations (79% in adults >65 years) and almost 9,000 deaths (93% in adults >65 years) (5). Moreover, it is well known the association between RSV infection in early life and the development of recurrent wheeze and asthma (6).
After only 4 years from RSV isolation in the early 1960, immunization of sero-negative infants for RSV with a virus inactivated in formalin was a disaster. 80% of the infants who receive the vaccine were hospitalized with a severe form of bronchiolitis with two deaths after wild infection. Two hypotheses were done: the vaccine stimulated a good antibodies production, but they were not neutralizing with a consequent immunocomplexes production; the vaccine predisposed to a hyper sensibility reaction with a Th2 response after reinfection with the wild RSV. This was supposed for the presence of an abundant number of eosinophils in the lungs of the two infants who died after the wild infection (7). Since then, de-spite more than 60 years of studying it is still not available a safe vaccine against RSV. The difficulties that have encountered with RSV vaccines research depend on the fact that the vulnerable population are infants in the first months of life and

the elderly adults with co-morbidities and that most of the population have immunity against the virus (8). One strategy to immunize infants, is mother immunization in the third trimester of pregnancy with a vaccine that is able to booster the preexisting mother immunity in order to transmit neutralizing antibody to the neonate. Similarly, a vaccine performed in the first months of life of the infant should be able to stimulate a good production of neutralizing antibodies preventing the hypersensitivity reaction. Today, six different types of vaccine, all using RSV pre-F protein are under research: subunit based, particle based, recombinant vector, chimeric, live attenuated and mRNA based (4) and four of these are in phase 3: two in the mother during the third trimester of pregnancy and two in young adults (9). Recently, it has been published the result of a phase 3 double blind study conducted in 18 countries in pregnant women from 24 through 36 weeks' gestation (10). The results showed a significant reduction of medically attended severe RSV associated LRTI in infants who receive the vaccine compared to the control group during 90, 120, 150, 180 months of follow up. Encouraging results come also from a recent phase 1 study on mRNA-based vaccine in young adults showing a good immunological response and few side effects (11).

What do we have today or are going to have in the short future to prevent RSV infection? Primary prevention (hand hygiene, face mask use, avoid close environment with many people, closure of schools and kindergartens, breast milk feeding and avoidance of passive smoke) that was strictly performed during COVID-19 epidemic is a good example on how it is possible to dramatically reduce respiratory virus epidemics (12). However, what it is happening with respiratory virus infection epidemics after the interruption of the lockdown for COVID-19, seems to suggest that virus circulation is necessary to maintain a level of trained immunity in the population in particularly of the innate immune response (13).

Now days, the only medical possibility to prevent RSV infection is the availability in the market of a monoclonal antibody, Palivizumab. It is a neutralizing monoclonal antibody direct against site II of the post-F protein. It was approved by EMA and AIFA in 1998 after the IMPACT study that have showed a 55% reduction of RSV hospitalization in premature babies (<35 weeks of gestational age) or with bronchopulmonary dysplasia (14). This antibody has several important limitations: 1. It is direct against site II of the post-F protein, that have a low affinity for neutralizing antibodies; 2. It has a short half-life, and this is the reason why it is administered once a month for 5 consecutive months starting from the beginning of RSV epidemic; 3. Its efficacy starts after the second-third administration. This antibody has been approved only for premature neonates or for neonates with special comorbidities. Another monoclonal antibody against site IV of the post-F RSV protein is actually in phase 3. This antibody, Clesrovimab, has shown to have a high equipotent potency against RSV group A and group B. The FC region of the antibody is engineered with 3 mutations for half-life extension and for this reason it is necessary to be administered only once during RSV epidemic (15).

The short future for RSV prevention for all neonates is probably Nirsevimab a monoclonal antibody that has passed phase 3 and was recently approved by EMA (16) and it is already inserted in the immunization calendar for all children in Spain (17). Nirsevimab has an advanced technology, it is an IgG1 monoclonal antibodies produced by human B lymphocytes with a high neutralizing capacity because it is direct against site 0 of the RSV pre-F protein and the FC region is engineered with the inclusion of new amino acids to prolog half-life (18). The highlights of this monoclonal antibody are that just one dose is necessary for the protection of all neonates during all the RSV season, it reaches an immediate protection just after its administration and it has a fix dosage (50 mg in infants less 5 kg of body weight and 100 mg in infants <5 kg). It is studied not only for neonates with bronchopulmonary dysplasia and congenital heart disease but for all neonates and infants during the first RSV season. Two recently published studied, have demonstrated the capacity of this monoclonal antibody to prevent medical attended RSV LRTI (pediatrician consultation and hospitalization) in preterm, late preterm and term infants (19-20). The main problem at the moment is the cost of the antibody that will allow its utilization in all neonates to prevent RSV infection during the first RSV season. The future of RSV prevention is behind the door and hopefully it is very close to come! RSV prevention in early life will have a strong protective effect not only in severe RSV infection in all infants, but also on the development of long-lasting sequelae such as recurrent wheeze and asthma.

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