European Journal of Pediatrics (2019) 178:131–138
https://doi.org/10.1007/s00431-018-03310-7

REVIEW

New therapies for acute RSV infections: where are we?

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Received: 13 September 2018 / Revised: 13 December 2018 / Accepted: 17 December 2018 / Published online: 4 January 2019
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Abstract

Respiratory syncytial virus (RSV) infection is one of the main causes of infant hospitalization and mortality. The single-stranded RNA virus codes for 11 proteins of which the F protein, a surface epitope responsible for RSV fusion, is the most targeted for developing antiviral medicines and vaccines. The peak of symptoms occurs around day 4 to 6 of illness and the airway obstruction is merely caused by the host immune inflammatory response. Risk factors for severe bronchiolitis are prematurity, comorbidity, and/or being immunocompromised. At present, there are no curative therapies available for RSV infections and treatment is supportive only. Development of new antiviral medicines is however promising. The aim of this review is to give a summary of the most important new antiviral therapies in clinical development for RSV infection and to explain their mode of action. We therefore performed a literature search on this topic.

Conclusion: There are currently at least eight antivirals being investigated in clinical trials. They all use different approaches to either focus on preventing viral fusion with host cells or inhibiting virus replication. Some target RSV surface epitopes like the F protein to halt fusion, others aim for RNA chain termination, while small interfering RNAs downregulate viral protein production.

What is known:
- *RSV bronchiolitis is a very important pediatric disease as it is one of the main causes of infant hospitalization and mortality. By the age of 2 years, 95% of all the infants worldwide will have been infected.*
- *The only recommended therapy is supportive since there are no existing curative therapies yet.*

What this study adds:
- *This review gives an overview of the current progress in the research field of RSV antivirals with background information on their mode of action.*

Keywords RSV · Bronchiolitis · Antiviral medication-mode of action

Abbreviations

AAP	American Academy of Pediatrics
AE	Adverse effects
BOS	Bronchiolitis obliterans syndrome
CMP	Cytidine monophosphate
Ig	Immunoglobulin
IVIG	Intravenous immunoglobulin
LRTI	Lower respiratory tract infection
miRNA	MicroRNA
NICE	National Institute for Health Care and Excellence
RISC	RNA-induced silencing complex
RNAi	RNA interference
RSV	Respiratory syncytial virus
siRNA	Small interfering RNA
SNP	Single-nucleotide polymorphism
TEAE	Treatment-emergent adverse effects

Communicated by Peter de Winter

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Introduction

General

Respiratory syncytial virus (RSV) is the most common cause of acute respiratory tract infections in infants [20, 38]. Over 95% of all children in the world have been infected with RSV by 2 years of age. RSV bronchiolitis is one of the leading causes of hospital admission of infants under 2 years of age worldwide and contributes greatly to the mortality rate in

those infants [23, 31]. The majority of these deaths (99%) occur in developing countries [34], while in countries like the USA, the majority of the deaths are associated with co-morbidity [6]. Hospitalization rates are the highest between 30 and 90 days after birth, a period that coincides with the concentration drop of the trans-placental acquired maternal antibodies [24, 32].

Bronchiolitis is generally defined as the first episode of wheezing in infants younger than 1 year of age and symptoms usually peak around 4 to 6 days of illness [32]. Other clinical features include nasal congestion, rhinorrhea, cough, tachypnea, wheeze, and increased respiratory effort. Bronchiolitis can also result in irritability and poor feeding but fever only occurs in approximately 50% of the infected infants. The course of bronchiolitis is variable and ranges from mild and transient airway symptoms to progressive respiratory distress. Apnea may be an early manifestation, especially in the first 2 months of life and in preterm infants [32, 38]. Severe bronchiolitis is usually defined as the need for respiratory support (requiring oxygen or ventilation) and the need for hospitalization [43].

So far, no curative therapies for RSV infections are available; however, multiple antivirals are in development and being tested in clinical trials. The main focus of this review is to give a summary of the most important new antiviral therapies that are currently in clinical trials for RSV infection and explain their mode of action.

Virus

RSV is a negative sense single-stranded RNA virus. Its genome codes for 11 proteins of which G and F (surface transmembrane proteins) play a key role in RSV binding and fusion respectively (Fig. 1). While the G protein is antigenically variable, the F protein is highly conserved but has a different pre- and post-fusion conformational structure with unpredictable switching [45].

SH (small hydrophobic) protein is an ion channel. M (matrix) protein forms the inner envelop. The viral nucleocapsid consists of another four proteins: N (nucleoprotein) binds the RNA, P (phosphoprotein and polymerase cofactor) and L (polymerase) are required for a functional RNA polymerase complex, and M2-1 (anti-termination protein) is a transcription factor. M2-2 is hypothesized to regulate virus replication [23, 31]. The two remaining proteins NS-1 and NS-2 (non-structural proteins) play an important role in escaping the innate immune responses, which includes interfering with interferon induction, as well as downregulating viral RNA synthesis [22, 23].

RSV strains are classified in two antigenically distinct subtypes (RSV-A and RSV-B) mainly different in the G protein (50% genetic differences) and less in the F protein (10% genetic differences) [45].

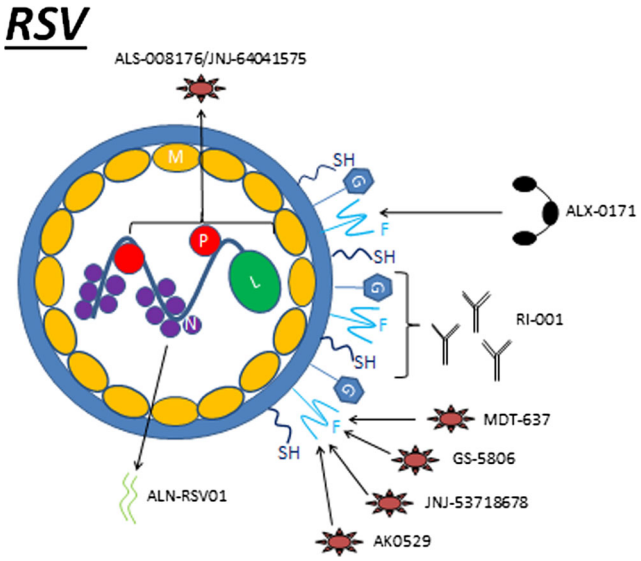

Fig. 1 RSV targets and antivirals. The arrows indicate which RSV protein(s) the antivirals target. ALS-008176/JNJ-64041575 targets the whole polymerase complex of P, N, and L while ALN-RSV01 is only a siRNA targeting N-mRNA. RI-001 is a polyclonal antibody that targets various RSV surface epitopes. The F protein is targeted by multiple antibodies (ALX-0171) and antivirals (MDT-637, GS-5806, JNJ-53718678, and AK0529)

Of all these viral proteins, G and F are the most targeted surface epitopes in the development of vaccines, neutralizing antibodies and (small) molecules, especially the F protein. The licensed profylaxis "Palivizumab" is directed against the RSV F fusion protein. Other possible therapeutic target proteins are L, N, and P [23, 31].

RSV is a RNA virus which implies that proofreading mechanisms to edit mutations in genome transcripts do not exist. The latter facilitates the generation of single-nucleotide polymorphisms (SNPs) and other mutations leading to changes in virus virulence and development of potential drug resistance to antiviral agents or vaccines [1].

The epidemiology of RSV has been postulated to resemble that of influenza B virus, with genetic changes occurring in response to selective pressure. Although in mRNA viruses, this antigenic variation may also occur in the absence of immune selection [44]. With respect to the therapeutic window, RSV is an easier target than influenza because the peak of viral load occurs 6–8 days post-infection [23].

RSV pathology

RSV is a relatively weak cytopathic virus and most of the airway damage situated in the bronchi and bronchioles is caused by the inflammatory host immune response [23, 32]: the lower airway obstruction is caused by mucus, mucosal swelling, and cell debris rather than due to bronchospasm [2, 29].

The prevention of infection, control of viral replication, and clearance of RSV infection are mediated by neutralizing antibodies generated by the humoral immune response together with the Th1 cell-mediated immune response [23, 32].

There seems to be a link between having RSV lower respiratory tract infections (LRTI) as a child and later development of recurrent childhood wheeze and asthma [23, 31, 40].

Risk factors

Risk factors for severe RSV bronchiolitis include prematurity, low birth weight (< 2.500 g) [7], genetic and chromosomal abnormalities, underlying immunologic disorders, cardiopulmonary comorbidity, neoplasia, and immunodeficiency [21, 23, 33].

Preterm infants carry a higher risk of severe RSV infections because they miss the period of greatest maternal IgG transfer in the third trimester of pregnancy [32]. Additionally, very young children are more susceptible to severe RSV infection because developing airways have a high surface area-to-volume ratio and their relatively smaller bronchial lumens are thus more prone to obstruction [23, 25, 36].

Environmental factors that can aggravate the severity of RSV infection are smoke exposure (cooking and tobacco), lower socioeconomic status, and overcrowding [23].

Adults and elderly

RSV infections recur during the whole lifespan. In adults, RSV infections predominantly present as upper airway infections except in patients with an underlying risk factor such as chronic pulmonary or circulatory disease, immunodeficiency, or frailty where lower airway infections can occur [23, 39, 46].

The declining immune system and lower RSV-specific immunoglobulin (Ig) as well as nasal IgA titers in the elderly make them more susceptible for RSV infections.

Prophylaxis and vaccines

At present, Palivizumab is the only prophylactic therapy available for RSV. It is a humanized monoclonal antibody directed against a conserved epitope on the RSV F fusion protein and needs to be administered monthly during the RSV season. Efficacy to prevent severe RSV infections has been mainly documented for premature infants and babies with cardiopulmonary disorders [23, 27, 32]. Since Palivizumab is not a treatment for acute infection, the need for curative remedy remains.

After a controlled clinical trial with a formalin-inactivated RSV virus in 1960 led to more severe RSV disease and two deaths, the clinical development of vaccines has been slower and more prudent [23, 31]. The balance between vaccine strain virulence and the immunogenicity is delicate [23, 32]. There are currently several vaccines in development using different approaches [31], but this is beyond the scope of this review.

Clinical management of RSV infection

Ribavirin is the only licensed drug to treat patients with RSV infection. However, due to unproven effectiveness and suspected teratogenicity, it is not used in clinical routine nor included in the American Academy of Pediatrics (AAP) guidelines [23, 38]. Both the AAP guidelines and The National Institute for Health and Care Excellence (NICE) guidelines agree on supportive management only which consists of respiratory support and hydration (Table 1) [18, 31, 35]. Unfortunately, bronchodilators, epinephrine, and corticosteroids are still too often used in clinical care even though there is no evidence for real benefit (Table 1).

Methods

For the literature search, the following mesh terms were applied in Pubmed and Limo for 2012–2017: “RSV, therapeutics, LRTI, viral bronchioles, and children.” In a second step, the reference lists of the retrieved articles and reviews were screened to complete the list of the aforementioned found articles including publications older than 5 years.

For information about the clinical trials themselves, the official database of all clinical trials worldwide (clinicaltrials.gov) and the EU clinical trial register (clinicaltrialsregister.eu) was consulted.

For this review, both of the “American Academy of Pediatrics Clinical practice guideline” as well as the “National Institute for Health and Care Excellence guideline” were also consulted [23].

Therapeutic antivirals

There are as yet no therapies that shorten the course of the disease or hasten the resolution of symptoms. One obstacle in drug development may be that during RSV replication, viral genetic changes such as SNPs and other mutations may occur, allowing the virus to escape antiviral therapies and vaccines [1, 23]. Another obstacle is the target group consisting of young babies with an acute illness, a group difficult to approach for early phase clinical trials. Nevertheless, multiple antivirals are in different stages of development.

We found eight different experimental antiviral strategies being explored in clinical trials. Each drug has its own intended target(s) (Fig. 1). The RSV antivirals can be divided into four classes, namely: immunoglobulins, nucleoside

Table 1 American Academy of Pediatrics guidelines and National Institute for Health and Care Excellence guidelines' recommendations

	American Academy of Pediatrics (AAP) guidelines	The National Institute for Health and Care Excellence (NICE) guidelines
Albuterol or salbutamol (bronchodilator medication)	Strongly not recommended. Multiple trials have failed to show consistent benefit from α- or β-agonist administration in pediatric patients with bronchiolitis. (2,22)	Not recommended. (21)
Epinephrine	Strongly not recommended. (2)	Not recommended. (21)
Systemic or inhaled corticosteroids	Strongly not recommended. No real effect was proven. (2)	Not recommended. (21)
Antibiotics	Not recommended. In the absence of specific evidence for concurrent bacterial infection, giving standard antibiotics to RSV infection patients is not recommended. (2,3)	Not recommended. (21)
Hypertonic saline	Not recommended in emergency settings. (2) Weakly recommends administration to patients with a hospital stay of longer than 3 days. However, 4 trials published after the publication of this guideline found no real benefit of using such therapy. (2,4)	Not recommended. (21)
Oxygen supplementation	Not recommended when SpO2 > 90%. (2)	Recommended when SpO2 < 92%. (21)
Nutrition and hydration	Recommended for infants with bronchiolitis who cannot maintain hydration orally. (2)	Recommended for infants with bronchiolitis who cannot maintain hydration orally. (21)

SpO2, peripheral capillary oxygen saturation

analogues, small interfering RNAs (siRNA)-interference (anti-sense), and fusion inhibitors (Table 2).

Immunoglobulins

ALX-0171 is a trivalent nanobody that inhibits the virus internalization by targeting the RSV F protein (both the pre- and post-fusion conformation) and is being developed as a treatment for acute RSV infection. This stable nanobody is derived from camelids who make heavy-chain-only antibodies that differ in architecture from human antibodies. In vitro, ALX-0171 is superior both in potency and in strain coverage when compared to Palivizumab. It neutralizes more efficiently a larger panel of RSV-A and RSV-B isolates, resulting in viral titers below the lower limit of detection. Nebulization is the most optimal route to efficiently deliver the ALX-0171 nanobody, allowing a high concentration of drug delivered straight at the site of infection to ensure a fast onset of action [8–10].

Between 2012 and 2013, three successful phase I trials were completed by Ablynx in adults. The drug was well tolerated and no dose-limiting toxicity or treatment-emergent immunogenicity was observed. In 2016, the first phase II study in RSV-infected infants and toddlers up to 23 months old was completed and following these results, recruitment was started for two new phase II studies in a similar population (clinicaltrials.gov) [8, 9].

RI-001 is an intravenous immunoglobulin (IVIG) preparation of pooled human plasma containing high titers of neutralizing anti-RSV antibodies. It targets the RSV surface epitopes G, F, and SH. RI-001 has antiviral as well as anti-inflammatory effects. It is anticipated that immunocompromised patients will benefit more from this therapy compared to immunocompetent ones. Administration early in the disease course is recommended for greatest benefit. In one study, RI-001 was perceived to be safe and caused minimal adverse effects (AE). Administration instigated at least a fourfold rise in the RSV neutralizing titers [17].

In 2010, ADMA Biologics completed a successful phase II trial in immunosuppressed RSV-infected patients aged 2 to 65 years. There was overall a dose-dependent rise in circulating RI-001 titer compared to baseline and a fourfold increase in serum neutralizing antibodies in the high dose group. The safety profile was very good (clinicaltrials.gov; no statistical analysis provided).

Nucleoside analogues

Nucleoside analogues are a class of medicines containing a synthetic nucleoside resembling a natural nucleoside but designed to be preferentially incorporated in the viral DNA or RNA, resulting in inhibition of viral enzymes and viral replication.

ALS-008176 is the prodrug of the potent and selective RSV polymerase inhibitor ALS-008112, a cytidine nucleoside

Table 2 Overview of RSV antivirals in clinical trials. All have been tested in adults and some in children

Name	Mechanism	Clinical trial	Adults	Children	
Antiviral: antibodies					
ALX-0171	Nanobody against antigenic site II of F	Phase 2	Yes	Healthy: yes	Sick: recruiting
RI-001	Ig against RSV	Phase 2	Yes	Healthy: no	Sick: yes
Antiviral: nucleoside analogue					
ALS-008176/ JNJ-64041575	Nucleoside analogue against RSV polymerase	Phase 2	Yes	Healthy: no	Sick: recruiting
Antiviral: anti-sense					
ALN-RSV01	siRNA against N-mRNA	Phase 2	Yes	Healthy: no	Sick: no
Antiviral: fusion inhibitors					
MDT-637	Antiviral against F	Phase 1	Yes	Healthy: no	Sick: no
JNJ-53718678	Antiviral against F	Phase 2	Yes	Healthy: no	Sick: suspended
GS-5806	Antiviral against F	Phase 2	Yes	Healthy: no	Sick: withdrawn
AK0529	Antiviral against F	Phase 1	Yes	Healthy: no	Sick: recruiting

analogue. It can be given orally thanks to its high orally bioavailability. In the respiratory tract, ALS-008112 is phosphorylated to its 5′-triphosphate metabolite (ALS-8112-TP), a formation that is crucial for its antiviral activity. In vitro, this metabolite is a pan-strain inhibitor of RSV replication acting by RNA chain termination. ALS-8112-TP competes with cytidine monophosphate (CMP) for incorporation into RSV RNA transcripts causing an immediate termination of chain synthesis [11, 15]. Important for safety, ALS-8112-TP did not inhibit human DNA and/or RNA polymerases, including the mitochondrial polymerase [11, 47].

Between 2013 and 2015, three successful phase I trials were completed by Alios BioPharma/Janssen Pharmaceutical in healthy adults. In 2014, a phase II viral challenge study was conducted in adults. The drug was safe and had important antiviral effects resulting in the reduction of clinical symptoms. In 2016, a phase II study was conducted in RSV-infected adults. Currently, the name ALS-008176 has changed to JNJ-64041575. In 2018, Janssen completed a phase I study in infants up to 12 months hospitalized for RSV bronchiolitis and started recruiting for two phase II trials, one in children up to 36 months and one in adults. The recruitment for these two phase II trials (one pending protocol amendment and one pending data analysis) is currently suspended (clinicaltrials.gov) [15].

RNA interference

Small interfering RNAs (siRNAs) are double-stranded RNA fragments functioning as a natural mechanism of protein synthesis downregulation. The mechanism of action is sequence-specific neutralization of posttranscriptional mRNA. The same mechanism can be applied using custom-made siRNAs with therapeutic aim [12, 13].

ALN-RSV01 is a siRNA directed against the mRNA encoding for the RSV nucleocapsid protein (N-protein). The siRNA prevents RSV N-protein synthesis through binding and cleavage of its mRNA (Fig. 2). In vitro, ALN-RSV01 has an antiviral effect against both of the RSV strain subtypes A and B [12, 13].

In 2006, Alnylam successfully completed two phase I trials in healthy male adults [3]. One year later, a phase II in healthy adults inoculated with RSV was completed. The aerosolized ALN-RSV01 had a statistically significant antiviral effect with lower rates of infection after inoculation and if infected, lower symptom scores [13]. Between 2009 and 2012, two phase II studies were completed in lung transplant patients with acute RSV infection. ALN-RSV01 was safe, well tolerated, and caused no treatment-emergent immunogenicity. Although it had no clear antiviral effect, it did improve the daily total symptom score and most importantly decreased the rate of new or progressive bronchiolitis obliterans syndrome (BOS) which is the equivalent of transplant organ rejection (clinicaltrials.gov) [19, 48].

Fusion inhibitors

The RSV F protein is essential for fusion of the viral membrane with the host-cell plasma membrane, leading to infection of the host cells. Therapeutic small molecules have been developed that bind the RSV F glycoprotein and inhibit membrane fusion.

MDT-637 (previously called VP14637) is a small molecule that reduces RSV replication by inhibiting the RSV F protein, although the exact mechanism of action is not known yet [16]. In vitro, MDT-637 is multiple times more potent than Ribavirin and has antiviral effects against a wide panel of RSV genotypes.

Between 2011 and 2012, MicroDose Therapeutx performed two successful phase I studies in healthy adults. The

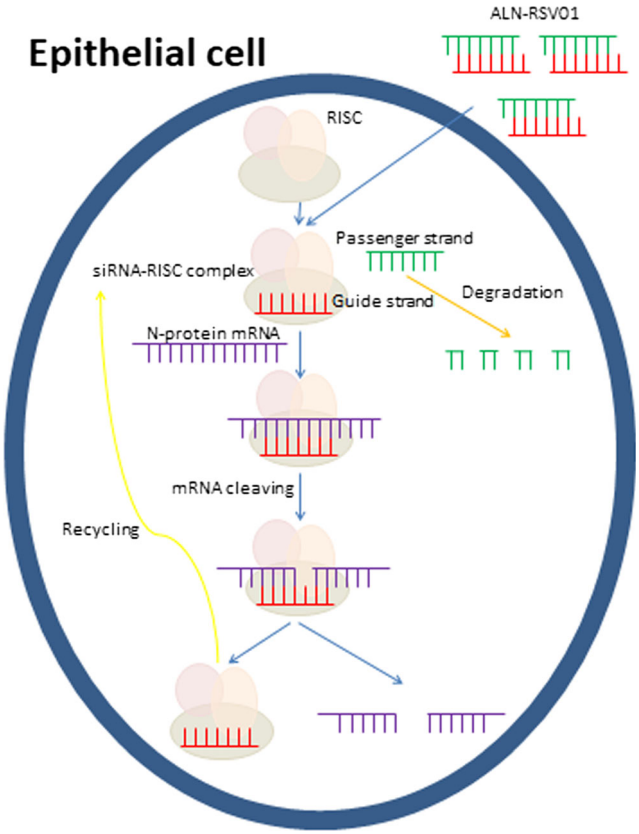

Fig. 2 ALN-RSV01 mechanism of action. The RNA-induced silencing complex (RISC) is a multiprotein complex involved in RNA interference (RNAi), a key process in gene silencing, and defense against viral infections. The two strands of ALN-RSV01 separate before the ALN-RSV01 guide strand integrates into the RISC. This complex incorporates a strand of single-stranded RNA fragments such as microRNA (miRNA), or double-stranded small interfering RNA (siRNA) to recognize the complementary mRNA. Once found, the complementary N-protein mRNA is cleaved. Afterwards, the complex is recycled. The two strands of ALN-RSV01 separate ALN-RSV01 integrates into the RNA-induced silencing complex (RISC), a complex that incorporates a strand of single-stranded RNA fragment and uses it for template to recognize complementary mRNA. The siRNA-RISC complex is formed with the guide strand and the passenger strand gets degraded. The complex then binds to the N-protein mRNA, cleaves the mRNA, and consequently releases the cleaved pieces. Afterwards, the complex is recycled

oral drug was well tolerated and caused no significant AEs (clinicaltrials.gov) [30].

JNJ-53718678 is a small molecule that tightly binds to a symmetric central cavity inside the pre-fusion F protein. This way, the conformational folding of the pre-fusion F protein into its post-fusion structure is prevented and no cell fusion will take place. This highly RSV-specific fusion inhibitor has very potent pan-strain antiviral activity and displays low cytotoxicity. In vivo, oral treatment with JNJ-53718678 led to dose-dependent decrease of RSV viral titers and a risk reduction of RSV-induced lung inflammation [41].

Between 2015 and 2017, Janssen successfully completed two phase I trials in healthy adults. The drug caused no serious treatment-emergent adverse effects (TEAEs) [26]. In 2015, Janssen also completed a phase II trial in healthy RSV-inoculated adults. The drug was well tolerated and generally safe. Antiviral activity as well as decrease in total symptom and symptom duration was documented [28]. In 2017, a phase I study in RSV-hospitalized infants aged 1 to 24 months was started. The drug had an established antiviral activity and caused lower symptom scores and mucus production. However, no dose-related relationship could be detected. The trial was early suspended (reason not communicated). In 2018, new recruitments were started for two phase II studies, one in RSV-hospitalized infants and one in RSV-infected adults (clinicaltrials.gov) (clinicaltrialsregister.eu).

GS-5806 is a small-molecule fusion inhibitor targeting the RSV F protein in its pre-fusion state. It interferes with the conformational change from pre- to post-fusion F by binding to the symmetric central cavity of pre-fusion F, just like JNJ-53718678, MDT-637, and most other fusion inhibitors do [5, 41, 42]. However, it does not share the same binding site with Palivizumab and thus maintains its activity against Palivizumab-resistant variants [42]. GS-5806 targets a wide panel of RSV clinical isolates comparable to other fusion inhibitors (MDT-637, Palivizumab, and Ribavirin) [37] and exhibits low cytotoxicity in many human cell types [42].

In 2013, Gilead completed a successful phase I study in healthy adults but a phase I trial in RSV-hospitalized infants up to 24 months was withdrawn without further information. Between 2013 and 2017, five phase II studies in adults were completed: three studies in adult transplant patients with RSV infection, one in adults hospitalized with RSV infection, and one in healthy adults inoculated with RSV. The oral drug was safe, well tolerated, and decreased the disease severity as well as the viral titer (clinicaltrials.gov) [14].

AK0529 is another potent pan-strain RSV fusion inhibitor targeting the F protein.

In 2015, Ark Biosciences Inc. completed a phase I in healthy adults. The oral drug had an excellent safety profile, was well tolerated, and caused no serious AEs [4]. One year later, in 2016, a phase I study in infants aged 1 to 24 months hospitalized for RSV infection was terminated (again for unknown reason). However, in the same year, Ark Biosciences Inc. started recruiting for a phase II in RSV-infected infants aged 1 to 24 months. In 2018, two new phase I trials were successfully completed in healthy adults, though no study results have yet been posted anywhere (clinicaltrials.gov).

Conclusions

Despite better knowledge on the RSV viral genetics, structure, the transmission, and replication, there are still no antiviral treatments on the market.

However, multiple antiviral strategies are currently being developed and tested in clinical trials. The antiviral researches focus mainly on preventing RSV fusion with the respiratory epithelial cells as well as inhibiting viral replication. The RSV F protein is the most targeted protein in the different drug development pipelines.

The investigational drugs use different approaches. Nanobodies and small-molecule fusion inhibitors target the F protein to prevent viral fusion with host cells, while antibodies target multiple RSV surface epitopes. The mechanism of action of nucleoside analogues is termination of chain synthesis and siRNAs downregulate viral protein production. Drug administration route is mostly oral or inhaled.

Research in this field is challenging for different reasons. The RSV virus is an unstable virus prone to SNPs and other mutations. Additionally, the target group is acutely ill young infants, a difficult group for phase I and II studies. As pediatricians, we have to prevent that promising new drugs are only tested in adults. Information to parents as well as pediatricians worldwide on the importance of these drug pipelines is important to achieve the necessary inclusion in clinical trials. Only then, the development of a curative therapy that is safe to use has a strong and lasting antiviral effect and instigates a higher level of protection than natural immunity, will become a reality in the future.

Authors' contributions Ying Xing performed the literature search and selection of articles with supervision of Marijke Proesmans. The first article draft was written by Ying Xing. Marijke Proesmans extensively worked with her towards the final draft.

Compliance with ethical statements

Conflict of interest Ying Xing has no conflict of interest to declare. Marijke Proesmans is the principal investigator for the drugs JNJ-53718678 and ALX-0171.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study: not applicable for this type of manuscript.

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