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Mini-Review

Respiratory syncytial virus (RSV) disease and prospects for its control

Philip R. Wyde *

Department of Microbiology and Immunology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

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Abstract

Respiratory syncytial virus (RSV) is a major virus pathogen of infants and young children, an important cause of disease in adults and is responsible for a significant amount of excess morbidity and mortality in the elderly. It also can be devastating in immunosuppressed populations. Vaccines are being developed, but none are currently licensed. Moreover, even if one or more are approved, they may not be suitable for some populations vulnerable to RSV (e.g. very young infants and the immunosuppressed). Ribavirin and immunoglobulin preparations with high titers of RSV-specific neutralizing antibodies are currently approved for use to treat and prevent RSV infection. However, neither of these is cost-effective or simple to administer. New agents are needed to reduce the impact of RSV. This review is concerned with the means currently available for controlling RSV, the search for new agents effective against this virus, and future prospects for preventing and treating RSV infections.

Keywords: Antivirals; Chemotherapy; Immunoglobulins; Respiratory disease; Ribavirin; RSV

1. RSV and the populations most vulnerable to RSV infections

Respiratory syncytial virus (RSV) belongs to virus family Paramyxoviridae, subfamily Pneumoviridae (McIntosh and Chanock, 1990). It has a lipid envelope and a genome consisting of a single negative-stranded RNA. As might be expected of a virus with its name, RSV grows primarily in the ciliary epithelial cells lining the respiratory tract (Gardner and McQuillan, 1974).

RSV was first isolated in humans in 1957 (Chanock et al., 1957). Within a short period of

* Tel.: +1 713 7985255; fax: +1 713 7986802; e-mail pwyde@bcm.tmc.edu

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time it was recognized as one of the most important causes of lower respiratory tract disease in infants and children worldwide (Chanock and Finberg, 1957, Gardner, 1973, Glezen and Denny, 1973, Kim and Arroyo, 1973, Medical Research Council Subcommittee on Respiratory Syncytial Virus Vaccines, 1978, Martin et al., 1978). The virus is ubiquitous and virtually all children are infected with RSV by 6 years of age (McIntosh, 1987). Their chance for exposure is great since RSV epidemics occur annually (Brandt et al., 1973, McIntosh and Chanock, 1990).

RSV has been divided into two subgroups, A and B. Classification into these groups is based on the reactivity of the strain in question with panels of monoclonal antibodies directed against epitopes on the fusion (F) and attachment (G) proteins that comprise the protective coat of RSV (Anderson et al., 1985, Akerlind et al., 1988). During epidemics, one subtype, or co-circulation of both subtypes, can occur (Hendry et al., 1986, 1988, 1989, Finger et al., 1987, Mufson et al., 1987, 1988, Hall et al., 1990). Differences in the severity of illness caused by the two subtypes have not been observed in most studies (Hendry et al., 1989, Mlinaric-Galinovic et al., 1994). Infection with a virus belonging to one subgroup does appear to provide some protection against reinfection with a virus from that group (Mufson et al., 1988). However, reinfections are common, suggesting that immunity following natural infection is incomplete (Ditchburn et al., 1971, Johnson et al., 1998). Moreover, in adults, where virtually all infections are reinfections, significant illness and appreciable morbidity can occur regardless of which subtypes they were initially infected with (Hall et al., 1978)

Although the majority of RSV infections are subclinical or mild, the total number of serious cases can be imposing (McIntosh, 1987). In the USA, the virus has been reported to be responsible for 40–50% of hospitalizations for bronchiolitis and 25% of pediatric hospitalizations for pneumonia (La Via et al., 1992). Many of these children may develop hyperactive airway disease and diminished pulmonary function later in life (La Via et al., 1992). The medical impact of RSV may be greater in developing countries than in developed ones (Selwyn, 1990).

Transmission of RSV is through large droplets, via fomites, or by direct contact with secretions (Hall et al., 1980, Hall and Douglas, 1981). Nosocomial infections and outbreaks in institutions can be explosive and may be introduced and spread by institutional personnel (Sims et al., 1975, Garvie and Gray, 1980, Hart, 1984, Finger et al., 1987, Englund et al., 1991). In these outbreaks, attack rates $>40\%$ are not uncommon (Garvie and Gray, 1980, Hart, 1984). The incubation period for RSV is 3–5 days and the clinical symptoms can vary widely (McIntosh, 1987, McIntosh and Chanock, 1990). Upper respiratory tract symptoms generally precede lower respiratory tract symptoms by 1–3 days (McIntosh and Chanock, 1990). More serious RSV infections generally occur in children less than 2 years of age (Groothuis et al., 1990a). Most at risk are infants less than 6 months of age (Bruhn et al., 1977, Medical Research Council Subcommittee on Respiratory Syncytial Virus Vaccines, 1978, Glezen et al., 1981), those with underlying pulmonary (McIntosh et al., 1973, Abman et al., 1988, Groothuis et al., 1988) or cardiac disease (Hall et al., 1985), and those with transient or chronic immunodeficiency states (Hall et al., 1986, Selwyn, 1990, Chandwani et al., 1990, King et al., 1993). Children undergoing transplantation (Solomon et al., 1981, Krowka et al., 1985, Martin et al., 1988, Hertz et al., 1989, Harrington et al., 1992, Sable and Hayden, 1995, Whimbey et al., 1996, Bowden, 1997, Englund et al., 1997) or receiving chemotherapy for leukemia (Whimbey et al., 1995b) are especially vulnerable. In these populations, mortality rates as high as 100% in untreated patients with RSV-induced pneumonia have been reported (Whimbey et al., 1996). Even in treated transplant and leukemia patients, the mortality rate in those who develop RSV pneumonia can exceed 50% (Whimbey et al., 1995b, 1996). The following summary (from Whimbey et al., 1996) provides an example of just how serious RSV can be in these populations.

> From 1 November 1992 through 1 May 1993, respiratory viruses were isolated from 36% of 102 bone marrow transplant recipients followed. The following year, from 1 November

1993 through 1 May 1994, 26% of 115 patients had respiratory virus isolated from them. Approximately half (49%) of these infections were due to RSV. Influenza virus (18%), picornaviruses (18%), parainfluenza virus (9%), or adenvovirus (6%) were isolated from the rest. Fifty-eight percent of the patients with RSV infections developed pneumonia and 51% of these died. Virtually all of these deaths were shown to be exclusively viral in origin (i.e. not complicated by secondary bacterial or fungal infections). The mortality rate was 100% in patients not promptly treated with antival agents. These results differed markedly from what was seen in the patients infected with the other respiratory viruses. Most of the pneumonias involving these viruses were either self-limited, or had associated bacterial or fungal infections.

Although it has long been known that RSV can infect adults and cause serious disease (Hall et al., 1978, Vikerfors et al., 1987), it was not appreciated until recently that RSV infections may be a major cause of hospitalization in this population (Dowell et al., 1996). Indeed, several reports indicate that RSV may be as important as influenza viruses in causing excess morbidity and excess deaths in the elderly (Agius et al., 1990, Fleming and Cross, 1993, Falsey et al., 1995).

2. Prevention of RSV infections: vaccines and immunoprophylaxis

2.1. Vaccines

Efforts to develop a safe and efficacious RSV vaccine for children began soon after identification of the virus. In the 1960s, clinical testing of the first of these, a formalin-inactivated, whole-virus vaccine, was begun. Despite much optimism, the effort did not end well (Fulginiti et al., 1969, Kim et al., 1969). Although many of the children receiving the vaccine produced virus-specific neutralizing antibodies, they were not protected from natural infection. Worse, many appeared to develop more severe disease when infected with RSV from the community than did unvaccinated children similarly infected.

The failed formalin–vaccine tests stimulated efforts to produce live RSV vaccines. Several of these were produced and entered into clinical trials. The results obtained were variable and generally discouraging (Kim et al., 1973, Wright et al., 1976, 1982, Richardson et al., 1978, Belshe et al., 1982). Parenteral immunization with wild-type virus induced virus-specific antibody responses in some vaccinated children, but generally did not seem to provide good protection against naturally acquired infection (Belshe et al., 1982). Intranasal administration of temperature-sensitive live RSV vaccines proved to be safe and efficacious in adults, but caused fever and ear infections in infants with low antibody levels. More attenuated temperature-sensitive vaccines were developed, but these failed to be sufficiently immunogenic (Kim et al., 1973, Wright et al., 1982).

In recent years, advances in molecular biology and biotechnology have spurred the development of numerous new and different RSV vaccine preparations. These include: RSV inactivated by ultraviolet light (Reuman et al., 1990); cold-adapted and temperature-sensitive, live attenuated RSV (Watt et al., 1990, Crowe et al., 1993, 1994, Randolph et al., 1994); preparations containing RSV subunits (Brideau et al., 1989, Wathen et al., 1991, Belshe et al., 1993, Homa et al., 1993, Oien et al., 1994); recombinant viruses producing RSV proteins containing protective epitopes (Wathen et al., 1989, Collins et al., 1990, Crowe et al., 1993, Brandt et al., 1997). Plasmid DNA expressing RSV viral proteins, RSV cDNA and negative-strand RSV genomic RNA have also been developed (Crowe, 1995, Murphy and Collins, 1997). Of these, testing of glycoprotein subunit vaccines is most advanced (Tristram et al., 1994, Piedra et al., 1995, 1996, Falsey and Walsh, 1997, Groothuis et al., 1998). However, despite the imposing number of candidate vaccines and approaches, it is not assured that any will be licensed soon, or be utilizable in all vulnerable populations (Pirofski and Casadevall, 1998). For example, although some of these candidate vaccines may prove to be efficacious in healthy indi-

viduals, they may not work well in infants with maternal antibodies to RSV (Englund and Glezen, 1991) or in individuals with immature (infants), diminished (the elderly) (Powers et al., 1995), deficient (the immunocompromised) or little (immunosuppressed) immune function. Hyperimmunizing pregnant women to provide protection to infants may provide an answer for this population (Englund and Glezen, 1991), and nucleic acid vaccines offer exciting possibilities in general. However, the latter are relatively new and their long-term safety is not yet known, particularly in the aforementioned populations.

2.2. Immunoglobulins

The slow progress made in the development of efficacious RSV vaccines led to attempts to use immune serum globulins (ISG) as a means of preventing RSV infection. Testing of these preparations was carried out incrementally and with great caution, primarily due to the population targeted (i.e. infants) and the fear of causing exacerbated disease. (See Groothuis (1994) and Ottolini and Hemming (1997) for comprehensive reviews on the use of ISG to prevent RSV infections.)

Initial attempts to prevent RSV infections using ISG utilized standard commercially available immunoglobulin preparations (Groothuis et al., 1991, Meissner et al., 1993). However, the virus-specific neutralizing antibody titers in these preparations proved to be variable and generally insufficient to raise the serum neutralizing antibodies in recipients to protective levels (Hemming et al., 1987). Higher titered immunoglobulin pools were identified and tested for safety in high-risk infants and children (Groothuis et al., 1993, Meissner et al., 1993). These preparations appeared to be well tolerated and a trend towards less severe RSV disease as measured by the number of days of hospitalization was observed. However, as in the previous trials significant protection from natural infection was not observed.

Immunoglobulin pools were then prepared using serum obtained only from donors who had demonstrably high RSV neutralizing antibody titers (Siber et al., 1992). The resulting pools were designated as respiratory syncytial virus immunoglobulin (RSVIG) and given monthly to recipients intravenously. RSV infections in the children given the RSVIG were not different from those that did not receive this preparation (Groothuis et al., 1993, 1995, PREVENT Study Group, 1997). However, in the groups administered the highest dose of RSVIG, there were measurable reductions in both the incidence and severity of RSV lower respiratory tract disease (i.e. 63% reduction in hospitalizations and hospital days, and 97% reduction in intensive care unit (ICU) days). However, similar reductions in the incidence and severity of lower respiratory tract infections were not observed in a similar study (Simoes et al., 1996).

Regardless of the benefit that RSVIG and similar preparations provide recipients, infusion of antibodies has limited utility. First, the procedure requires multiple visits and a hospital setting. Second, there is some risk associated with the relatively large volumes of globulin that must be administered to achieve benefit. Third, the cost to patients is very high (estimated to exceed $5000 per season) (Ottolini and Hemming, 1997).

Attempts have been made to overcome these liabilities by producing high titered monoclonal antibody (mAb) preparations to RSV that can be used in humans (Walsh et al., 1984, Tempest et al., 1991, Taylor et al., 1995). Since such preparations ordinarily have higher concentrations of RSV-specific neutralizing antibodies in them than serum preparations, it may be possible to administer them intramuscularly and in smaller fluid volumes than serum immunoglobulins, and still achieve protective levels of circulating antibodies. A number of different mAb preparations have been produced, including HNK20 (an IgA mAb), RSHZ19 (a humanized mouse (IgG) mAb) and Medi-493 (also a humanized mouse (IgG) mAb). In animal studies, all three preparations exhibited good antiviral efficacy (Weltzin et al., 1994, 1996, Taylor et al., 1995, Wyde et al., 1995a, Johnson et al., 1997). However, only Medi-493 has exhibited protective efficacy in clinical trials (Medimmune, Inc., 1997, Oravax, Inc., 1997).

3. Therapeutic approaches for treating RSV infections

3.1. Immunoglobulins

At least three studies evaluating the therapeutic efficacy of RSVIG have been performed (Hemming et al., 1987, Rodriguez et al., 1997a,b, PREVENT Study Group, 1997). In two of the studies, reduced hospitalization and days in the ICU were seen in the groups treated with RSVIG compared to the control groups. However, the differences observed were not statistically significant. In the third study, no differences in duration of hospitalization or duration of ICU stay were noted (Rodriguez et al., 1997b). Neither was there a difference in the requirement for supplemental oxygen or use of mechanical ventilation between the treated and untreated groups.

3.2. Ribavirin

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a nucleoside analog of guanosine that has been licensed since 1986 for use to treat serious RSV disease when administered as an aerosol (Committee on Infectious Diseases, 1993). Despite this approval, the mechanisms of action by which this compound inhibits RSV are not well known. Ribavirin is known to inhibit influenza virus replication following monophosphorylation by: (1) competitively inhibiting inosine monophosphate dehydrogenase, leading to a reduction in guanosine triphospate pools required for viral transcription (Wray et al., 1985a); (2) preventing 5′ capping of mRNA, a step essential for influenza virus-dependent, as well as host cell transcription of mRNA (Goswami et al., 1979, Gilbert and Knight, 1986); and (3) interfering with virus-specific RNA polymerase initiation and elongation steps required for the synthesis of essential viral proteins (Eriksson et al., 1977, Wray et al., 1985b). It is likely that the first and last of these mechanisms are also involved in ribavirin's inhibition of RSV. Other sites of virus replication may also be affected in addition to these. Support for the concept that ribavirin acts at multiple sites of virus replication, comes from the fact that RSV mutants resistant to this nucleoside analog have not been found even following prolonged use of this drug (Hayden, 1996).

Approval of ribavirin aerosols to treat RSV disease by the Food and Drug Administration was based on data obtained in one preclinical (Hruska et al., 1982) and a number of clinical studies (Hall et al., 1983a,b, 1985, Taber et al., 1983, McIntosh et al., 1984, Barry et al., 1986) that indicated that ribavirin could inhibit RSV replication, improve clinical scores and increase oxygen saturation in children with lower respiratory tract infection. Since the drug's approval, other positive studies (Conrad et al., 1987, Rodriguez et al., 1987, Smith et al., 1991), including those involving children with chronic lung disease (Griffin et al., 1995) and immunocompromised individuals (Englund et al., 1988, Harrington et al., 1992, Sparrelid et al., 1997), have been published. However, an equally impressive number of articles have been published since 1989 indicating that ribavirin has minimal or insignificant effects on RSV disease, mortality or duration of hospitalization (Groothuis et al., 1990b, Janai et al., 1993, Wheeler et al., 1993, Meert et al., 1994, Law et al., 1995, Moler et al., 1996, Ohmit et al., 1996, Lewinsohn et al., 1996). These apparently conflicting results have lead to contention about the validity of using ribavirin to treat RSV disease (Snell, 1990, Wald and Dashefsky, 1994, Randolph and Wang, 1996). Adding to the controversy are the high cost of ribavirn treatment (estimated in 1994 to average $3300 per case; Englund et al., 1995, Nelson and Englund, 1996) and the apparent need to administer this compound using very long treatment schedules (typically 12 h or more per day of continuous aerosol; Nelson and Englund, 1996).

In an attempt to improve the efficacy of ribavirin, it has been tested in combination with ISG in both animals (Gruber et al., 1987) and humans (Whimbey et al., 1995a, DeVincenzo et al., 1996) in an attempt to improve the efficacy of this drug. Results have been encouraging, although the latter studies lacked sufficient controls to properly evaluate the results obtained.

Attempts have also been made to shorten the duration of the daily aerosolization times used for

ribavirin treatments. The results obtained in animal studies have been remarkable. In these studies, equivalent reductions in pulmonary RSV titers were seen in groups of cotton rats exposed to 'high' doses (i.e. 60 mg/ml reservoir concentration) of ribavirin twice daily for 2 h as were seen in groups of cotton rats administered standard doses of this compound (i.e. 20 mg/ml reservoir concentration) for 12 h each day (Wyde et al., 1987). Significant reductions in pulmonary RSV titers were also observed in animals exposed to ribavirin aerosols twice daily for 30 min (Gilbert et al., 1992). 'High-dose, short-duration' ribavirin studies also have been carried out in children (Englund et al., 1990, 1994) and adult bone marrow transplant (BMT) patients (McColl et al., 1998). However, because the former studies were designed primarily to assess safety and efficacy, groups of children receiving standard doses of ribavirin were not included in them. It is thus difficult to determine if the protection seen was comparable to what would have occurred had the children received the standard treatment. Control groups were also not included in the adult BMT study. However, given the history of RSV in this population, the results were impressive; all of the patients administered the short duration nebulized ribavirin made a full recovery.

Regardless of whether one does or does not believe that ribavirin can be used to successfully treat RSV disease, it should be apparent from the preceding discussion that there is a need to identify new, more effective, less costly and more easily delivered chemotherapeutic agents to treat or prevent RSV infections.

4. New antivirals

4.1. Chemotherapeutic agents

Although overshadowed by the interest in RSV vaccines, ISGs and ribavirin, there has been a sustained effort to find new and better agents that can effectively prevent or control RSV infections. Much of this effort has been directed at identifying new chemotherapeutic compounds, in particular those that inhibit the earliest steps of viral replication (i.e. virus attachment, penetration and uncoating), and those that interfere with steps required for viral RNA transcription and translation (see Tables 1–3). De Clercq (1996) has a comprehensive review on this subject.

Table 1
A partial list of compounds that inhibit RSV attachment to the host cell

Compound(s)	Reference(s)
Carboxymethyl dextrans	Neyts et al., 1995
Benzylamide substituted dextrans	Neyts et al., 1995
Sulfonated dextrans	Neyts et al., 1995
Polyoxometalates	Shigeta et al., 1995, Barnard et al., 1997
Polysulfonates	Hosoya et al., 1991, Ikeda et al., 1994
Polysulfates	Witvrouw et al., 1994, Hasui et al., 1995
(Heparin)	Hosoya et al., 1991
Algal extract	Hasui et al., 1995
SP-303	Gilbert et al., 1993, Wyde et al., 1993a,b

4.2. Compounds that inhibit RSV attachment, penetration and/or uncoating

A number of compounds have been reported to inhibit attachment of RSV to host cells (see Table 1). Included in this group are carboxymethyl, benzylamide and sulfonated dextrans (Neyts et al., 1995), polyoxometalates (Shigeta et al., 1995,

Table 2
A partial list of compounds reported to inhibit RSV entry and/or virus uncoating

Compound(s)	Reference(s)
Bis(5-amidino-2-benzimidazolyl)methane	Dubovi et al., 1980
Mono- and diamidines	Dubovi et al., 1981
Pyridobenzoazoles	Shigeta et al., 1992, Chiba et al., 1995
Substitued imidazo [1,5-a]-1,3,5 triazine	Kolocouris et al., 1994
Amantadine-like compounds	Kolocouris et al., 1994
CL387626	Wyde et al., 1998

Table 3
Representative compounds that inhibit RSV transcription and translation and their targeted enzymes

Compound	Enzyme inhibited	Reported SI	Reference(s)
Ribavirin	IMP dehydrogenase	>50–100	Sidwell et al., 1972, Kawana et al., 1987, De Clercq et al., 1991a, Shigeta et al., 1992
Ribamidine	IMP dehydrogenase	>62	Gabrielsen et al., 1992
EICAR	IMP dehydrogenase	>2000	De Clercq et al., 1991a, Shigeta et al., 1992
Neplanocin A[a]	SAH	>2000	Shuto et al., 1992
Cc3Ado	SAH	85	Wyde et al., 1990
Pyrazofurin	OMP decarboxylase	1071	Kawana et al., 1987
PALA	L-ATCase	72	Wyde et al., 1995b
CPC (Ce-Cyd)	CTP synthetase	>10 000	De Clercq et al., 1991a

SI, selective index; IMP, inosine monophosphate; SAH, *S*-adenosylhomocysteine hydrolase; L-ATCase, L-aspartic acid transcarbamoylase; OMP, ornithine monophosphate decarboxylase; CTP, cytosine triphosphate; EICAR, (5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide; PALA, *N*-(phosphonoacetyl)-L-aspartate; CPC, cyclopenylcytosine.
[a] Neplanocin A and derivatives of this compound.

Barnard et al., 1997), polysulfonates (Hosoya et al., 1991, Ikeda et al., 1994) and polysulfates (including heparin and heparin derivatives) (Hosoya et al., 1991, Witvrouw et al., 1994, Hasui et al., 1995). An extract of the marine microalga, *Cochlodinium polykrikoides* (Hasui et al., 1995), and SP303, a distillate of an euphorbiaceae shrub (Gilbert et al., 1993, Wyde et al., 1993b), have also been reported to block virus attachment. Although many of these compounds exhibit potent inhibition of RSV in tissue culture cells, few have been tested against this virus in animals. Of those that have, antiviral efficacy has generally been seen only if the compounds were administered at about the same time as virus (Wyde et al., 1993a, Ikeda et al., 1994).

A number of compounds ostensibly prevent virus penetration and entry into the host cell. Included in this group are bis(5-amidino-2-benzimidazolyl)methane (Dubovi et al., 1980), mono- and diamidines (Dubovi et al., 1981) and pyridobenzoazoles (Chiba et al., 1995). Substituted imidazo[1,5-a]-1,3,5-triazine and a series of amantadine-like compounds (e.g. *spiro*[cyclopropane-1,2′-adamantan]-2-amines and methanamines) (Kolocouris et al., 1994) also fall into this category. As with the agents that affect attachment, many of these compounds exhibit significant antiviral activity against RSV in tissue culture assays, but have not, in general, been tested against this virus in animal models. A compound in this group that has been evaluated in animals is the Wyeth Ayerst compound CL387626 (4,4′bis[4,6-di[3-aminophenyl-*N*,*N*-bis(2-carbamoylethyl)- sulfonilimino]-1,3,5-triazine-2-ylamino-biphenyl-2,2′ disulfonic acid, disodium salt). CL387626 is noteworthy for three reasons: (1) its prophylactic activity lasts for days; (2) it is efficacious following topical administration; and (3) it has been shown to be efficacious in animal studies. In these studies, single 30 mg/kg doses of CL387626 administered intranasally to cotton rats 4 or 5 days prior to virus challenge significantly inhibited pulmonary replication of RSV compared to the pulmonary virus titers seen in placebo-treated animals (Wyde et al., 1998).

Because compounds that inhibit virus attachment and/or penetration generally must be present in relatively high concentrations at the time of virus infection, most are not practical for use in clinical situations. However, their extraordinary antiviral activity and low cytotoxicity in tissue culture assays (i.e. many have selective indices >1000) make them of continuing interest.

In addition, it may be possible to find derivatives of these compounds, or related drugs, that may prove to be effective in vivo. It is also conceivable that their efficacy could be enhanced by administering them topically (e.g. intranasally or by aerosol).

4.3. Compounds that inhibit RNA transcription and translation

Nearly all of the antiviral agents that are currently licensed (amantadine and rimantadine being the primary exceptions) have been shown to inhibit steps essential for transcription, reverse transcription or translation of viral nucleic acid. Thus it is not surprising that much effort has been expended on finding compounds that block RSV replication by inhibiting cellular enzymes essential for transcription or translation of the virus genome. As indicated in Table 3, a number of cellular enzymes have been targeted, including inosine monophosphate dehydrogenase (De Clercq et al., 1991a, Balzarini et al., 1993), *S*-adenosylhomocysteine hydrolase (Sidwell et al., 1972, De Clercq, 1987, Wyde et al., 1990, Gabrielsen et al., 1992, Shigeta et al., 1992, Patil et al., 1992, Shuto et al., 1992, Siddiqi et al., 1994a,b), L-aspartic acid transcarbamoylase (Wyde et al., 1995b), ornithine monophosphate decarboxylase (Kawana et al., 1987, Wyde et al., 1989) and cytosine triphosphate synthetase (De Clercq, 1994). Also listed in Table 3 are some of the compounds that have been found to inhibit these enzymes and suppress RSV replication in tissue culture assays. One of the more interesting of these compounds is EICAR (5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide), a derivative of ribavirin. The reported selective index (SI) of this compound suggests that it is 20–50 times more active against RSV than ribavirin (De Clercq et al., 1991a, Shigeta et al., 1992, Balzarini et al., 1993). Also of interest, because of their extraordinary SIs, are 6′-(*R*)-6′-C-methylneplanocin A ($SI > 2000$) (Shigeta et al., 1992), pyrazofurin ($SI = 1071$) (Kawana et al., 1987, Wyde et al., 1989) and cyclopentenylcytosine ($SI > 10000$) (De Clercq et al., 1991b). 5′-Noraristeromycin and two derivatives, 3-deaza- and 7-deaza-5′-noraristeromycin, are notable because the enantiomeric forms of these compounds exhibit markedly different antiviral activity (Patil et al., 1992, Siddiqi et al., 1994a,b, 1995).

Three other compounds that have been observed to have good selective antiviral activity in in vitro assays are 3-deazaguanine ($SI > 100$) (Kawana et al., 1987), 6′-diazo-5-oxo-L-norleucine ($SI > 1000$) (Huang et al., 1994) and 5′-deoxypyrazofurin ($SI > 42$) (Chen et al., 1993). However, the mechanism(s) by which these compounds inhibit RSV replication are not clear.

Despite the number of chemotherapeutic agents listed above that have shown good selective antiviral activity in preclinical testing, none are likely to enter soon clinical trials, or be licensed for use to control RSV infections. To begin with, several of these compounds have exhibited toxicity in in vivo testing (e.g. pyrazofurin (Wyde et al., 1989), neplanocin A (Shuto et al., 1992) and PALA (Wyde et al., 1995b)), making them unacceptable for clinical use against RSV, particularly in infants and young children. Second, most of these compounds, including such promising ones as EICAR and cyclopentenylcytosine, have not been tested in animals for either antiviral efficacy or toxicity. Although the forecast for the immediate future is not bright, it is better for the not too distant future. This optimism is based on a number of factors: (1) several of the compounds listed above (e.g. EICAR and cyclopentenylcytosine) have exhibited very good antiviral activity in tissue culture assays and should begin testing in animals; (2) CL387626 has done well in initial animal studies and seems ready for more extensive preclinical testing; (3) based on presentations at antiviral meetings and the activity of this and similar laboratories, there are a number of new compounds in the 'pipeline'; and (4) in recent years there have been numerous new approaches to drug discovery, including the rational design of antiviral agents (Alper, 1990, Anonymous, 1990, Luo et al., 1997, Kuntz, 1992, Whittle and Blundell, 1994), development of 'high-throughput' synthesis of compounds (Selway and Terrett, 1996), improved rapid antiviral screening and laboratory automation. All of these should significantly accelerate the discovery of new drugs. In addition to

these things, new or different delivery systems are being investigated, such as the use of liposomes (Six et al., 1988) and topical delivery (Wyde et al., 1996, 1998). Improved delivery should increase the antiviral efficacy and/or reduce the toxicity of antiviral compounds.

4.4. Immune modulators

Although the production of immune modulators following RSV infection of mice, humans or cells from these species has been well studied, only a few studies have looked at the effects of immune modulators on RSV replication or virus-initiated immunopathology. Connors et al. (1994) reported that the enhanced pulmonary histopathology seen in mice inoculated with formalin-inactivated RSV and then challenged with live RSV could be abrogated by depletion of interleukin 4 (IL-4) and IL-10. Similarly, Tang and Graham (1994) showed that anti-IL-4 treatment administered at the time of RSV vaccine immunization modulates cytokine expression, reduces illness and increases cytotoxic T-lymphocyte activity in mice challenged with RSV. These studies suggest that it may be possible to use immune modulators to ameliorate RSV-induced immunopathology and disease. However, interferon is the only cytokine that has been seriously evaluated for clinical efficacy (Chipps et al., 1993, Sung et al., 1993). Unfortunately, in neither of two trials was a significant reduction in RSV titer or disease observed.

Immune modulators that are not cytokines have also been studied. One, amiloride, has been shown to reduce IL-6 production in epithelial cells in a dose-dependent manner (Mastronarde et al., 1996). However, the effects of this compound on RSV infection were not evaluated. Superoxide dismutase (SOD) has been shown to reduce pulmonary virus titers in cotton rats experimentally infected with RSV (Wyde et al., 1996), and has also been reported to modulate the antiviral state induced in mice by alpha- and gamma-interferons (Raineri et al., 1996). In the cotton rat studies, animals administered recombinant (r) manganese (Mn) or copper–zinc (CuZn) SOD by continuous small particle aerosols had significantly reduced titers of RSV in their lungs than virus-infected animals not administered these recombinant molecules. The reduced pulmonary virus titers were observed only in cotton rats that were exposed to the continuous small-particle aerosols of rMn SOD or rCuZn SOD and not in animals administered the rSOD preparations intraperitoneally or intranasally. The protective effect was not due to direct inactivation of the virus, since in vitro, even doses as high as 1000 μg/ml of rMn SOD or rCuZn SOD did not inhibit virus.

4.5. Antisense oligonucleotides

Antisense oligonucleotides have also been considered as a means to control RSV infections, and have shown selective inhibition of this virus in tissue culture (Cirino et al., 1997, Jairath et al., 1997). However, there have been difficulties in successfully getting these molecules intact and in sufficient numbers to interact with targeted viral RNA. These difficulties have led researchers to try to develop better methods to direct the antisense oligonucleotides to the nucleus (Cirino et al., 1997) and to use catalytic mechanisms to effectively destroy specific mRNAs (Torrence et al., 1997).

5. Prospects for controlling RSV disease

It is clear that RSV continues to be a major human pathogen, despite more than 30 years of efforts to prevent and treat the lower respiratory diseases caused by this virus. Indeed, recognition of the virus' medical importance has expanded; RSV is no longer considered primarily a pathogen of children, but is also acknowledged as a significant cause of disease in adults with especial impact in the elderly and particular immunocompromised populations. However, despite the slow progress there are reasons to be optimistic that it may soon be possible to more effectively prevent and control infections caused by this virus. An array of RSV vaccines are being developed that may prove to be effective. In addition, regardless of whether or not an efficacious RSV vaccine is developed, there is an increasing likelihood

that new agents will be discovered to replace the two currently approved methods controlling RSV infections, ribavirin and immune serum globulins. This optimism is based both on the number of different approaches that are currently being followed (e.g. immune modulators, antisense oligonucleotides and chemotherapeutic agents), and the rapid advancement of technology. Compounds more active than ribavirin have already been identified and many more are likely to be elucidated because of the recent advances in drug discovery.

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