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Viral Respiratory Infections Due to Rhinoviruses: Current Knowledge, New Developments

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Viral respiratory infections (VRIs) are among the most common reasons for which primary care providers are consulted. VRIs due to rhinoviruses—the most commonly implicated etiologic agent—constitute a syndrome characterized by signs and symptoms of a cold. Rhinoviruses have been implicated in respiratory tract illnesses such as sinusitis and otitis media, as well as lower respiratory complications in high-risk populations. Most patients treat VRI with over-the-counter remedies that have been demonstrated to produce marginal clinical benefits. The development of novel antiviral agents has intensified interest in VRIs. Pleconaril, a capsid-function inhibitor currently under FDA review, has been shown in clinical trials to reduce the duration and severity of rhinovirus VRIs. By targeting the cause of illness, antiviral agents represent an opportunity to reduce the substantial clinical burden of VRI. Furthermore, effective therapies can potentially reduce inappropriate antibiotic use for viral infections.

Keywords: viral respiratory infections, rhinoviruses, symptomatic medication, antiviral therapy, pleconaril.

INTRODUCTION

Viral respiratory infection (VRI) is the most commonly occurring illness in humans. The pathogens primarily associated with respiratory infections include picornaviruses, coronaviruses, adenoviruses, parainfluenza viruses, influenza viruses, and respiratory syncytial viruses.[1]

The VRIs due to rhinoviruses constitute a syndrome characterized by signs and symptoms of a cold, or rhinosinusitis. Rhinorrhea, nasal congestion, and sore or scratchy throat are the most common presenting symptoms. Other less common symptoms include cough, sneezing, hoarseness, facial pressure, ear fullness, headache, and, less often, malaise and fever.[1]

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Despite the high incidence, substantial attributable morbidity, and the tremendous drain of VRI on productivity, these infections do not receive a great deal of attention when compared with other clinical conditions, primarily because of the lack of effective treatments.

The purpose of this article is to discuss the impact of VRIs; describe the most common organism associated with these infections, the rhinovirus; and review symptomatic therapy for VRIs (eg, herbal and homeopathic remedies). Finally, specific antiviral therapies that are under investigation are discussed.

PICORNAVIRUSES: THE MOST COMMON CAUSE OF VIRAL INFECTION

The picornaviruses together constitute the most common causes of infections in humans in the developed world. The rhinoviruses, a genus of the family Picornaviridae, are the most frequent pathogens involved in VRIs.[1] Picornaviruses are very small ("pico," approximately 27–30 nm in diameter) ribonucleic acid viruses consisting of a simple viral capsid and a single strand of RNA. The capsid contains four proteins,

VP1–VP4, arranged in 60 repeating protomeric units in an icosahedron (Fig. 1).[2] The discovery of the three-dimensional atomic structure of certain rhinoviruses was crucial to the development of specific antiviral agents.[3]

THE IMPACT OF VIRAL RESPIRATORY INFECTIONS

The VRIs are among the most common infections for which primary care providers are consulted. Depending on the source reporting, preschool-aged children experience, on average, five to seven colds per year, but 10% to 15% of children in this age group have at least 12 colds per year.[4] The incidence decreases with age to an average of 2 to 4 per year by adulthood.[4,5]

The National Institute of Allergy and Infectious Diseases of the National Institutes of Health estimates that as many as 1 billion colds occur annually in the United States. Although survey data are available, they vastly underestimate the scope of the problem. For example, survey data collected in 1996 by the National Center for Health Statistics reported 62 million cases of colds requiring medical attention, 27 million of which occurred in persons younger than 17 years.[5] There were approximately 22 million days of missed school, 20 million days of missed work, 148 million days of restricted activity, and 45 million bed-ridden days.[5] Recently, Gonzales et al[6] reported that there were 25 million office visits to primary care providers for nonspecific upper respiratory tract infections.

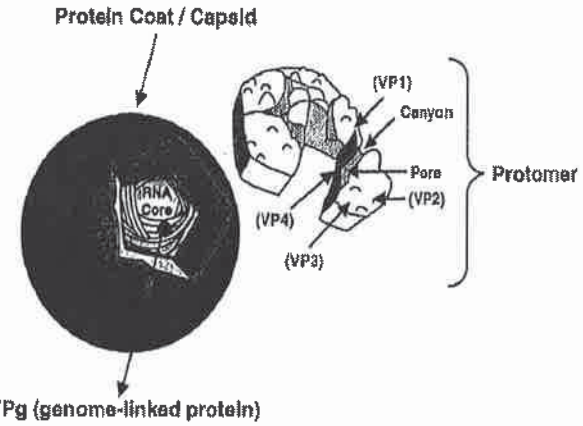

Fig. 1. Three-dimensional structure of a picornavirus. Picornaviruses are very small (approximately 27–30 nm in diameter) ribonucleic acid viruses consisting of a simple viral capsid and a single strand of RNA. The capsid contains four proteins, VP1–VP4, arranged in 60 repeating protomeric units in an icosahedron. (Adapted from Romero.[2])

These data should be considered the minimum impact statistics for the cold.

Direct medical costs associated with VRI are estimated to be approximately $16.8 billion annually (eg, physician visits $6 billion, complications $3.8 billion, prescription and over-the-counter medications $4.8 billion, other costs $2.2 billion).[7] Indirect costs, mostly measured as lost wages, approximate $7.6 billion per year. The vast majority of colds are self-treated.[8]

Perhaps just as important, upper respiratory tract infections represent one of the most frequent reasons for inappropriate and excessive antibiotic use in the United States,[9] which increases the costs of illness unnecessarily and contributes to the increasing prevalence of antibiotic-resistant bacteria.[10]

The clinical presentation of a VRI affects the decision by practitioners to prescribe antibiotics.[11] The common attributes of rhinovirus infection, which are discolored nasal discharge and postnasal drainage, are significantly associated with prescribing of antibiotics.[12] However, purulent nasal discharge and sputum do not predict bacterial infection, nor do they predict benefit from antibiotics.[11] Dosh et al[12] reported in a recent survey that antibiotics were prescribed for 66% of all patients with acute respiratory illnesses. Among patients with respiratory illnesses, 80% diagnosed with bronchitis received a prescription for antibiotics, 98% diagnosed with sinusitis received a prescription, and 21% diagnosed with nonspecific upper respiratory infection received a prescription. It is therefore important for clinicians to distinguish viral from bacterial infections to prescribe treatment appropriately, through use of proper respiratory indicators, and to minimize the selective pressure on common bacteria to develop resistance against antibiotic agents.

RHINOVIRUS EPIDEMIOLOGY

Worldwide, the distribution of rhinoviruses occurs in all ages and during all seasons, but infections are most prevalent in early spring and fall in temperate climates.[13] Seasonal changes such as school opening and crowding indoors may explain the seasonal prevalence.[14]

Two well-done studies support the seasonality of rhinovirus infection. Arruda et al[15] found picornavirus by cell culture or reverse transcription polymerase chain reaction (RT-PCR) in 82% (283/346) of adult patients who had self-diagnosed colds during the peak 2-month season study period of September through October. Makela et al[16] reported similar findings. During the peak 2-month outbreak in the fall months of

their study, rhinovirus was identified in 92% of the 200 young adults who had signs and symptoms of a cold.

Rhinoviruses are also responsible for respiratory tract complications such as acute otitis media, acute sinusitis (or rhinosinusitis), and exacerbations of asthma. In addition, rhinoviruses are directly or indirectly the cause of lower respiratory illnesses in certain populations (eg, those who have cystic fibrosis or are immunocompromised), and of exacerbations of chronic obstructive pulmonary disease in adults.[1] Recent RT-PCR techniques have increased the detection rates of rhinovirus in these complications and provide a more accurate picture of their role in the pathogenesis of these infections.[17]

RHINOVIRUS PATHOGENESIS, TRANSMISSION, AND CLINICAL ILLNESS

There are more than 100 different serotypes of rhinoviruses. In persons lacking specific immunity to the infecting serotype, most exposures result in infection.[1] Rhinovirus infections produce isolated scattered foci of infected nasal epithelium between large areas of normal epithelium.[18] Abnormalities of the paranasal sinuses are also frequently detected during rhinovirus infection.[1] The absence of histopathologic lesions during rhinovirus infection suggests that the virus itself does not appear to be cytotoxic and that the host response to the virus causes the symptoms.[18]

Rhinorrhea and nasal obstruction are due to increased vascular permeability, with leakage of serum into the nasal mucosa and nasal secretions.[18] Cold symptoms also are caused by neurologic reflexes triggered by the infection. Glandular secretions in the nose, under the control of cholinergic neurologic pathways, contribute to rhinorrhea, especially in later stages of the cold.[18] Neurologic pathways also appear to be involved in the reactive airway disease associated with rhinovirus infection.[1]

Inflammatory mediators such as interleukin (IL)-1β, IL-6, and IL-8 have been reported in nasal secretions of symptomatic subjects. Their concentrations increase and decrease as symptom severity increases and decreases.[4,18] The presence of inflammatory mediators has been taken into consideration in the development of therapeutic strategies.

There is some controversy about the principal mode of transmission for rhinovirus. However, direct contact appears to be the most efficient means of transmission.[4] Rhinovirus can survive for days on door handles, coffee cups, drinking glasses, and plastic surfaces.[19] Typically, when rhinovirus transmission occurs in the home, a school-aged child is the most frequent introducer of infection.[13] Infection is spread from hand-to-hand contact with contaminated nasal secretions, usually from child to mother or caretaker. Self-inoculation from eye-rubbing or nose-picking also spreads infection.[13]

Symptoms occur within 16 hours of experimental inoculation and peak 24 to 48 hours after inoculation. The virus can be recovered 24 hours after nasal inoculation, and shedding peaks on day 2 or 3.[13] Viral shedding persists after resolution of symptoms, and the virus can be cultured from 10% to 20% of subjects 2 to 3 weeks after infection.[4]

Arruda et al[15] found that sore throat, nasal congestion, and rhinorrhea were the first symptoms noticed in patients with naturally occurring colds. The most bothersome symptoms were runny nose, stuffy nose, sore throat, and malaise. Recognition of these symptoms early may be useful in initiating early therapy. Coughing, sneezing, hoarseness, facial pressure, and headache are also typical symptoms. Cough usually persists for 1 week but may be prolonged in smokers. Less often, malaise, chills, and low-grade fever may occur.[1,13] The median duration of rhinovirus colds is 1 week, but up to 25% last more than 2 weeks.[1] Arruda et al[15] found that colds in rhinovirus-positive patients lasted from 9.5 to 11 days and that symptom severity was highest on presentation and declined over the study period. Because the maximum burden of disease occurs within the first 3 to 4 days of infection, antiviral therapy is required early in the course of the disease for optimal benefit.

Currently, rhinovirus infections are diagnosed on the basis of clinical signs and symptoms. Because new antiviral medications will soon become available, rapid and accurate diagnosis is essential. Currently, no effective rapid antigen detection or practical serologic test exists for rhinovirus because of the numerous serotypes.[20] Viral isolation in tissue culture followed by acid-lability tests represents the standard laboratory method for confirmation of rhinovirus infections. However, this method requires up to 2 weeks for results to become available, limiting its value in clinical decision-making.[21]

The RT-PCR assay is more sensitive and rapid (results available in less than 2 days) than culture for viral identification. Steininger et al[21] found that RT-PCR detection of rhinovirus DNA in nasopharyngeal aspirates was positive for all samples that were rhinovirus-positive by culture isolation (100% sensitive),

but it also was positive in some of the culture-negative samples. At present, RT-PCR is only a research tool.

TREATMENT OF VIRAL INFECTION

Most VRI patients self-treat with symptomatic medications or herbal or homeopathic medications that have demonstrated modest and varied clinical benefit in well-controlled trials.[8] The wide variety of over-the-counter cold remedies available and the recent development of compounds with activity against rhinoviruses attest to the intensified interest in infections caused by this pathogen.

Alternative and Complementary Medications

Because of their popularity in recent years, a variety of herbal and homeopathic remedies have been tested in vitro and in controlled trials. Zinc, echinacea, and vitamin C are the most commonly used by patients suffering from colds. Reviews of controlled studies have failed to provide incontrovertible evidence that these agents are beneficial. However, these medications are reviewed as alternative remedies to treat VRIs.

Zinc salts have been found to inhibit rhinovirus replication in vitro, but the mechanism by which this occurs is unclear.[22] Turner and Cetnarowski[23] reported on two clinical trials of zinc gluconate or zinc acetate in experimental and natural rhinovirus colds. The median duration of illness in the zinc gluconate group was 2.5 days, versus 3.5 days in placebo group. Zinc gluconate had no enhanced effect on symptom severity, and zinc acetate had no effect on duration or severity.

Mossad et al[24] reported on a randomized, placebo-controlled trial of zinc gluconate lozenges (1 every 2 hours as long as patients had cold symptoms) in reducing the duration of symptoms caused by a cold. These symptoms were described as nasal, cough, and throat symptoms. Time to complete resolution of symptoms was significantly shorter in the zinc group (4.4 days versus 7.6 days). Side effects of nausea (20% versus 4%; $P = 0.02$) and bad taste (80% versus 30%; $P < 0.001$) were significantly greater in the zinc group. A meta-analysis of eight clinical trials of zinc gluconate lozenges concluded that evidence of effectiveness of zinc lozenges in reducing the duration of a cold is lacking.[22]

Two other recent studies have shown some benefit. Prasad et al[25] reported that administration of zinc acetate lozenges reduced the duration and severity of symptoms, especially cough. Hirt et al[26] reported that zinc nasal gel (an over-the-counter medication) was effective in shortening the duration of cold symptoms compared with placebo when it was taken within 24 hours of symptom onset (2.3 days versus 9 days; $P < 0.05$). However, methodologic problems limit the usefulness of this study. Recently, a zinc nasal spray has become available as an over-the-counter medication for cold symptoms, but overall, due to the lack of well-controlled clinical trials, the clinical utility of zinc in treating colds is still debatable.

Echinacea species plants have long been used by Native Americans for the treatment of a variety of diseases.[27] More recently, *Echinacea purpurea* has been used most frequently in Europe (particularly in Germany) as an immunostimulating agent for the prevention and treatment of various infectious disorders. Pharmacologic effects, mainly directed toward the nonspecific cellular immune system, have been found in vitro and in vivo. However, clinical benefit has not been definitely proven in randomized, controlled studies.

Turner et al[28] assessed the effectiveness of echinacea in preventing experimental rhinovirus colds. Rhinovirus infection occurred in 44% of patients who received echinacea prophylactically versus 57% of the placebo group ($P = 0.3$), and clinical colds developed in 50% and 59% ($P = 0.77$) of the echinacea- and placebo-treated subjects, respectively. Moreover, in virus-infected subjects, there was no statistically significant effect of echinacea on the daily total symptom score.

Grimm and Muller[27] reported on a placebo-controlled trial of fluid extracts of *Echinacea purpurea* twice daily or placebo to treat and prevent respiratory infections in 108 patients who had three or more colds or respiratory infections in the preceding year. The incidence and severity were determined during the 8-week study period. Treatment with echinacea did not significantly decrease the incidence, duration, or severity of VRIs, compared with placebo.

Although many cold sufferers use large doses of vitamin C, believing it to be valuable in reducing symptom severity and duration, its reported therapeutic benefit in alleviating or preventing colds has been inconsistent.[8] One review of 30 therapeutic trials of vitamin C concluded that doses of vitamin C of as much as 1 g daily for several months in the winter had no consistent beneficial effect on the incidence of the cold.[29] Preventive and therapeutic trials both showed a generally modest beneficial therapeutic effect on the duration of cold symptoms, but the effect was variable from patient to patient. In tests of vitamin C administered after the onset of cold symptoms, there was some evidence that large doses daily produced a greater benefit than lower doses.[29]

Symptomatic Medications

Symptomatic therapies for nasal congestion, rhinorrhea, sneezing, sore throat, and cough are still the mainstay of treatment (Table 1).[4] Nasal congestion and rhinorrhea appear to be the most bothersome symptoms for patients suffering from colds,[15] and the ones for which patients commonly seek medications.

Both topical and oral adrenergic agents are effective nasal decongestants, but intranasal decongestants are generally considered more rapid and effective than systemic agents.[4] Prolonged use of topical agents poses risk of a rebound effect when the drug is discontinued. Systemic side effects of oral agents are central nervous system stimulation, hypertension, and palpitations.[4]

Some of the symptoms treated with systemic medication include rhinorrhea, sneezing, cough, and sore throat.

Rhinorrhea is treated by blockade of cholinergic stimulation of glandular secretions.[2] The anticholinergic agent ipratropium bromide has shown modest efficacy in reducing rhinorrhea and is approved for treatment of rhinorrhea in colds.[30]

First-generation antihistamines such as clemastine fumarate[31] and brompheniramine maleate[32] have been used for rhinorrhea and sneezing and have shown modest benefit. Second-generation antihistamines are not effective.[4] The observed similarity in the effect of ipratropium and first-generation antihistamines on rhinorrhea is most likely related to the anticholinergic rather than antihistaminic properties of these drugs.[4]

Table 1. Current treatments for VRIs—symptomatic medications.

Symptom	Medications
Rhinorrhea	Anticholinergics (ipratropium bromide) 1st-generation antihistamines
Nasal congestion	Intranasal and systemic decongestants
Cough (therapy depends on cause of cough)	Nonspecific cough suppressants with codeine or dextromethorphan Antihistamine-decongestant if due to nasal obstruction or postnasal drip Bronchodilator if due to reactive airway disease
Sneezing	Antihistamine
Sore throat, myalgias, fever, headache	Mild analgesics, NSAIDs

Adapted from Turner.[4]

Cough during a cold is triggered by several different mechanisms, and therapy should be directed at the most likely underlying cause.[4] Nonspecific cough-suppressant medications containing either codeine or dextromethorphan are frequently used, but their clinical efficacy is based on studies of patients with chronic cough; their efficacy has not been consistently demonstrated in patients with colds. Cough due to nasal obstruction and postnasal drip can respond to an antihistamine-decongestant agent.[4] Cough caused by reactive airway disease induced by the virus may be prolonged, and the patient may benefit from bronchodilator therapy.[4]

Finally, sore throat during a cold is generally not severe and can be treated with mild analgesics or nonsteroidal anti-inflammatory drugs. These agents also alleviate systemic symptoms such as myalgia and headache.[4]

ANTIVIRAL THERAPIES FOR VIRAL RESPIRATORY INFECTIONS DUE TO PICORNAVIRUSES

Novel antiviral agents that attack the rhinovirus are either in development or in advanced clinical trials. These agents have the effect of reducing the severity and duration of symptoms of colds. In addition, complications of VRIs, such as acute otitis media, sinusitis, and exacerbations of asthma and bronchitis can potentially be reduced by these agents. Furthermore, reducing viral transmission can lessen the likelihood of transmitting the infection to others, thereby reducing the overall incidence of VRIs.[33] The ultimate result of antiviral medication use is a reduction in the prevalence and severity of bothersome symptoms and an improved quality of life for the sufferer. The mechanisms of action and the development status of these agents are summarized in Table 2. Knowledge of stages of the infection cycle has provided therapeutic opportunities (Fig. 2).[3,19] It is important to recognize that appropriate use of antiviral drugs to treat colds cannot be guided by rapid diagnostic tests for rhinovirus in the ambulatory setting, as office-based tests are not currently available and are not likely to be available in the near future.[10]

Interferons

Interferons are potent selective mediators of cellular changes that induce antiviral, antiproliferative, and immunologic effects on host-cell susceptibility to picornavirus infection.

Douglas et al[34] conducted a double-blind evaluation of intranasal alpha-2 interferon prophylaxis against

Table 2. Antiviral compounds under investigation.

Compound type or name	Mechanism	Status
Intranasal Interferon alpha-2	Antiviral, antiproliferative, immunologic effects affecting host-cell susceptibility	Side effects limit its use
Soluble ICAM-1 (tremacamra)	Blocks receptor site	Development discontinued due to marginal clinical benefit and frequent doses required
Enviroxime-related compounds	Targets 3A protein coding region of the virus to inhibit RNA replication, prevents formation of a new strand of RNA molecules	Early agents had only modest clinical benefits; new agents are under development
3C protease inhibitors (AG7088)	Inhibits viral protein synthesis	Phase II trials to recommence with reformulated compound that maximizes delivery of active ingredient
Capsid-function inhibitors (pleconaril)	Blocks viral uncoating and/or viral attachment to host-cell receptors	Clinically effective, NDA submitted July 2001; awaiting approval

NDA, New Drug Application.

naturally acquired rhinovirus infection in family members. Users of alpha-2 interferon who were exposed to rhinovirus infections experienced a 76% reduction in the number of days during which they experienced respiratory symptoms of any kind (6.3 versus 1.5), 33% fewer days with nasal symptoms (2.1 versus 1.4), and 86% fewer "definite" illnesses than placebo users (13 versus 2 family episodes).

Hayden and Gwaltney[35] reported on the efficacy of recombinant interferon alpha-2 administered as intranasal spray or drops given three times daily for 5 days beginning 28 hours after rhinovirus inoculation. Interferon alpha-2 did not prevent rhinovirus infections or colds but was associated with significant reductions in symptom duration (spray: 5 versus 7.6 days, $P < 0.01$; and drops: 3.8 versus 8.2 days, $P < 0.03$) and in quantity of viral shedding.

Another study compared intranasal alpha-2 interferon versus placebo begun within 48 hours of the onset of illness, to prevent respiratory illness in healthy contacts of ill family members.[36] Respiratory illness developed in 52 of 222 persons in the placebo group, compared with 32 of 226 in the interferon group ($P = 0.02$). In the 2-week period during and after spraying, rhinovirus colds developed in 1.3% of the treated group and in 15.1% of the placebo group.

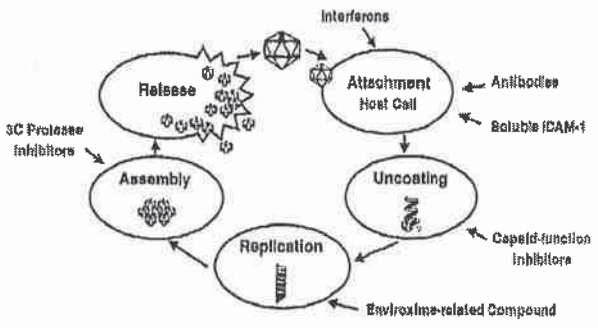

Fig. 2. Infection cycle of virus provides diagnostic and therapeutic opportunities. (Adapted from Rotbart.[3])

A combination of antiviral and anti-inflammatory agents provided better symptom relief than monotherapy with an antiviral agent.[37] Gwaltney[37] reported on the combination of intranasal interferon alpha-2, ipratropium, and oral naproxen begun 24 hours after experimental rhinovirus inoculation and continued three times daily for 4 days. The addition of anti-inflammatory agents to treat the inflammatory response addressed the previous therapeutic failures of monotherapy with antivirals (which only inhibit viral replication). Viral shedding was 4.4 days in the control group and 2.9 days in the treatment group ($P < 0.003$). Colds developed in 6 of 16 treated subjects and in 7 of 8 control subjects ($P = 0.05$). Symptom scores were also reduced for rhinorrhea ($P < 0.01$), cough ($P < 0.01$), and malaise ($P < 0.001$) in treated subjects.

Although intranasal interferon demonstrated clinical benefit in prophylaxis against rhinovirus colds, by reducing viral shedding and modestly reducing symptoms,[12] the side effects of nasal irritation and stuffiness and mucosal ulceration in some patients have prevented its further clinical development.

Soluble Intercellular Adhesion Molecule-1

Soluble intercellular adhesion molecule-1 has broad-spectrum activity against a variety of major rhinovirus serotypes.[38] Tremacamra is an intranasally administered recombinant soluble intercellular adhesion molecule-1 that was studied in clinical trials. In four randomized, placebo-controlled trials, two different intra-

nasal formulations were evaluated in 177 subjects treated 5 to 6 times per day 7 hours before or after viral challenge; 81 received tremacamra and 96 received placebo.[38] Pooled analysis from the four studies showed that, compared with the placebo group, the treatment group had a reduction in total symptom scores (17.6, placebo group versus 9.6, treatment group), in the proportion of clinical colds (64/96 [67%] versus 36/81 [44%]), and in nasal mucus weight (32.9 g versus 14.5 g) ($P < 0.001$ for all comparisons). No adverse effects were observed. However, the marginal clinical benefit observed in this highly controlled prophylaxis setting in which the drug was administered five to six times per day is the presumed reason for the discontinuation of tremacamra development.[39]

Enviroxime-related Compounds

Enviroxime is a prototype compound for a series of molecules with broad anti-rhinovirus activity. In vitro, it showed potent antirhinoviral activity against certain serotypes.[3] The mechanism of action is suggested to be inhibition of RNA replication via targeting of the 3A protein coding region of the viruses. This action prevents the formation of a new strand of RNA molecules. Early clinical studies of enviroxime demonstrated a modest clinical and antiviral benefit in some patients but no benefit in others.[3]

Phillpotts et al[40] tested enviroxime against rhinovirus infection in volunteers in early trials. There were no significant differences in reductions in total clinical scores, nasal secretions, and virus excretion, compared with placebo. The efficacy of intranasal enviroxime was also tested against naturally occurring colds.[41] There were trends indicating greater therapeutic efficacy of enviroxime for certain nasal symptoms (stuffy nose), but overall there were no consistent statistically significant differences between treated versus untreated groups.

Problems with poor pharmacokinetics, undesirable side effects, and toxicity resulted in the discontinuation of the enviroxime program. Newer derivative compounds have improved tolerability and bioavailability, but these compounds have not yet been clinically evaluated.[3]

3C Protease Inhibitors

A series of compounds are under development that target the 3C protease of picornaviruses and result in inhibition of viral protein synthesis.[3] Rhinovirus 3C protease is responsible for cleavage of viral precursor polyproteins into structural and enzymatic proteins essential for viral replication.[3]

Intranasal AG7088 is a potent, irreversible inhibitor of rhinovirus 3C protease and is the most advanced of these compounds. In vitro activity against rhinovirus demonstrated that AG7088 inhibited viral replication of all rhinovirus serotypes tested as well as rhinovirus in clinical isolates recovered from patients with colds.[42–44] Antiviral activity was present when the compound was added up to 26 hours after infection, demonstrating the potential for activity well after the onset of symptoms.

In adult experimental rhinovirus challenge prophylaxis studies, AG7088 or placebo was administered 6 hours before viral challenge and continued two or five times a day for 5 days.[45] In the prophylaxis studies, the proportion of individuals shedding virus was reduced in the two groups given AG7088. This was statistically significant in the group receiving AG7088 five times per day. The incidence of colds, total symptom scores, respiratory symptoms, and nasal discharge was also reduced, with a trend toward greater effects in those treated five times per day. For early treatment, administration was begun 24 hours after the challenge. In the early treatment studies, viral titers were reduced by day 2 or 3. Total symptom scores, respiratory symptoms, and mucus weights were significantly reduced, compared with the same measures in the placebo-treated group. AG7088 did not prevent experimental rhinovirus infection, but it modestly reduced illness severity when treatment was initiated before or within 1 day of infection, with administration five times per day. The most common drug-related adverse events (nausea and taste disturbance) were mild in severity.

In 1999, AG7088 was evaluated as a treatment of natural colds in a double-blind, placebo-controlled trial including 868 subjects.[46] The results revealed no evidence of a treatment benefit. Currently, the intranasal compound is being reformulated to optimize delivery of the active ingredient to the nasal cavity. Phase II trials will probably begin again with the reformulated compound.[39]

Capsid-function Inhibitors

Developments in this class of compound during the past decade suggest that capsid-function inhibition is a very promising antiviral therapeutic approach. Capsid-binding compounds block viral uncoating and viral attachment to host-cell receptors. Trials of the early intranasal compound pirodavir showed that it was efficacious when administered prior to the onset of symptoms in experimental colds.[47,48] However, its development was limited by its modest clinical benefit

and the fact that frequent daily doses must be administered. Results from these trials have led to work on other related compounds in this class.

Oral pleconaril (3-[3,5-dimethyl-4-[(3-methyl-5-isoxazolyl)propyl]phenyl]-5-(trifluoromethyl)-1,2,4-oxadiazole) is the first of a new generation of capsid-function inhibitors.[3] Pleconaril inhibits in vitro viral replication at the site of viral attachment and uncoating. It alters the ability of the virion to bind to cellular receptors and increases the stability of the viral capsid.[49]

Pleconaril displays potent activity against rhinoviruses and the structurally related enteroviruses. In vitro activity against selected rhinovirus serotypes and against clinical isolates recovered from patients with colds showed that antiviral activity inhibited 90% of rhinoviruses at concentrations well within the range of levels achievable in humans.[44] High-level drug resistance to one compound is generally seen for all related compounds.[50]

Phase II clinical trials showed that patients treated with pleconaril showed an overall reduction in overall illness and individual symptom duration and severity of 1 to 3 days compared with placebo.[51,52] This is the first demonstration that specific antiviral therapy can provide meaningful symptomatic benefit in persons with a picornaviral respiratory illness.

Phase III clinical data for pleconaril were recently reported. A randomized, double-blind, placebo-controlled evaluation of pleconaril 400 mg TID versus placebo for 5 days in 1044 otherwise healthy adults presenting with moderate or worse rhinorrhea and at least one other respiratory symptom of 24 hours' duration or less showed that, compared with placebo-treated subjects, rhinovirus-positive patients treated with pleconaril had a 1.5-day reduction in complete resolution of rhinorrhea with all other symptoms absent or mild for 48 hours (median 6.2 versus 7.7 days; $P = 0.001$), as well as a 25% reduction in mucus production, as measured by facial tissue use ($P < 0.001$).[53] Symptom severity was less in the pleconaril group each day, beginning 12 to 24 hours after initiation of therapy. Compared with placebo, there was a significant reduction in median viral titers in nasal mucus on days 3 and 6 among the pleconaril-treated patients ($P < 0.001$). Adverse event rates were similar between the pleconaril and placebo groups.

In all six Phase II/III clinical trials in a total of 4,447 adults, pleconaril was well tolerated.[54] The aggregate side-effect profile was similar to that of placebo. The majority of adverse events were mild to moderate; gastrointestinal events and headache were most commonly reported.[54] A New Drug Application for pleconaril was submitted in mid-year 2001.

CONCLUSIONS

Viral respiratory infections are among the most common clinical conditions encountered by primary care providers. Most of these infections are due to rhinoviruses. The degree of illness ranges from mild to severe. The high prevalence of uncomplicated illness and the attributable complications, which include acute otitis media, sinusitis, exacerbations of asthma and chronic obstructive pulmonary disease, and lower respiratory tract infections, demonstrate that these infections are responsible for a great deal of morbidity in all age groups. Thus far, only symptomatic medications and homeopathic remedies have been available. In general, these medications have not demonstrated significant clinical benefit. Until recently, no treatment targeted rhinoviruses, which are the most common cause of VRIs. Furthermore, there has been no rapid test to identify rhinoviruses in a clinically useful time frame.

New developments in antiviral therapy, such as the capsid-inhibitors for rhinovirus infections, represent an important opportunity to reduce the clinical burden of disease. Furthermore, use of a specific antiviral agent for VRIs can potentially reduce inappropriate antibiotic use and help in the nationwide effort to slow the increasing emergence of bacterial resistance.

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