Review

The treatment of rhinovirus infections: progress and potential

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The clinical syndrome of the common cold is caused by a variety of different viral pathogens. The rhinoviruses are the most frequent cause of these illnesses and may be responsible for as many as 80% of colds during the fall rhinovirus epidemic (Monto and Cavallaro, 1971; Johnston et al., 1995; Arruda et al., 1997). Other viral pathogens associated with the common cold are the coronaviruses, respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, and adenovirus. In contrast to the rhinoviruses, these agents are either responsible for a much smaller proportion of infections or are usually associated with lower respiratory or systemic symptoms in addition to the nasal symptoms characteristic of the common cold (Monto and Cavallaro, 1971).

Surveillance data suggest that both adults and children experience a rhinovirus infection every 1–2 years (Gwaltney et al., 1966; Fox et al., 1985). The rhinoviruses cause infection year-round but are associated with an increased incidence of illness in the fall and the spring of the year. The onset of common cold symptoms typi-cally occurs 1–2 days after viral infection and the time to peak symptoms is generally 2–4 days (Tyrrell et al., 1993). Nasal obstruction, rhinorrhea and sneezing are present early in the course of the cold, however, sore or 'scratchy' throat is frequently reported as the most bothersome symptom on the first day of illness (Tyrrell et al., 1993; Turner et al., 1996; Arruda et al., 1997). The sore throat usually resolves quickly and by the second and third day of illness the nasal symptoms predominate. Cough is associated with approximately 30% of colds and typically does not become the most bothersome symptom until later in the illness when the nasal symptoms decrease in severity (Gwaltney et al., 1967; Tyrrell et al., 1993). The usual cold lasts about a week, although 25% last 2 weeks (Gwaltney et al., 1967). Virus shedding persists after the resolution of symptoms and virus may be cultured from 10 to 20% of subjects for 2–3 weeks after infection (Winther et al., 1986).

Although the common cold is associated with little morbidity, the complications of these illnesses; otitis media, sinusitis and exacerbations of reactive airway disease have a substantial medical impact. In spite of the medical significance of the

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common cold and its complications, attempts to develop effective treatments have been relatively limited and unsuccessful.

The purpose of this review is to describe the current status of treatments for the common cold. Generally recognized goals of treatments for rhinovirus colds include amelioration of the symptoms of the illness, prevention of person-to-person spread of infection and prevention of the complications of the common cold. Currently available treatments are limited to symptomatic therapies. Although there are few new symptomatic treatments, the passage of the Dietary Supplement Health and Education Act in 1994 has prompted increased interest in herbal medicines and dietary supplements for common cold treatment. Substantial progress has been made in the development of antiviral treatments for rhinovirus, although none of these agents has been approved for use as treatment for the common cold. Finally, it is now widely accepted that the host response to the rhinovirus contributes to the illness associated with these infections. Recent advances in understanding the mechanism of the host response to rhinovirus infection have the potential to reveal new targets for the interruption of unwanted host responses as a treatment strategy for these illnesses.

1. The pathogenesis of rhinovirus colds

Rhinovirus is transmitted to a susceptible individual by either direct contact or large particle aerosols (Gwaltney et al., 1978; Dick et al., 1987). The virus then infects both ciliated and non-ciliated nasal epithelial cells (Bardin et al., 1994; Arruda et al., 1995). Although the nasal secretions from human volunteers infected with rhinovirus contain small numbers of rhinovirus infected and uninfected ciliated epithelial cells that have been sloughed from the mucosa (Turner et al., 1982), the infection appears to involve a very small proportion of the epithelium (Arruda et al., 1995). Examination of biopsy specimens of the nasal epithelium by either light or electron microscopy reveals no consistent lesions (Turner et al., 1982; Winther et al., 1984a,b, 1990). The absence of

detectable histopathology during rhinovirus infection led to the suggestion that the host response to the virus may play a primary role in the production of common cold symptoms (Turner et al., 1982; Hendley, 1983).

Evaluation of this hypothesis has produced compelling evidence that the host response plays a role in rhinovirus pathogenesis. The peripheral white blood cell count increases in rhinovirus-infected, ill subjects during the first 2–3 days after virus challenge (Douglas et al., 1966). This increase in the white blood cell count is the result of an increase in the concentration of circulating polymorphonuclear leukocytes (PMNs). Of note, subjects who are infected but not ill have no change in the peripheral white blood cell count. A similar PMN response to rhinovirus infection is seen in the nasal mucosa and nasal secretions (Winther et al., 1984b; Naclerio et al., 1988). As with the changes in peripheral neutrophil count, the increase in PMNs is seen in infected symptomatic subjects but not in infected asymptomatic individuals (Naclerio et al., 1988).

The observation that a PMN response in both blood and the nasal mucosa was associated with symptomatic infections led to efforts to understand the origin of this inflammatory response. Initial studies, conducted in vitro, found that infection of cell culture monolayers with rhinovirus resulted in elaboration of a chemoattractant for PMNs (Turner, 1988). Subsequent studies identified interleukin-8 (IL-8), a potent chemoattractant for PMNs, as at least one mediator of this chemoattractant activity (Subauste et al., 1995; Zhu et al., 1997). Studies with coronavirus, respiratory syncytial virus, adenovirus and influenza virus also demonstrate IL-8 elaboration from virus-challenged cells in vitro (Choi and Jacoby, 1992; Becker et al., 1993; Subauste et al., 1995; Bruder and Kovesdi, 1997; Kaul et al., 2000).

Studies in human volunteers have established an association between IL-8 and common cold symptoms. Increased concentrations of IL-8 are present in the nasal secretions of subjects with symptomatic rhinovirus infection and of children with common cold symptoms of undetermined etiology (Noah et al., 1995; Grunberg et al., 1997; Zhu et al., 1997; Turner et al., 1998). Further-

more, in experimental rhinovirus infection there is a direct correlation between the severity of common cold symptoms and the concentration of IL-8 in the nasal secretion (Turner et al., 1998). The observation that intranasal challenge of normal subjects with IL-8 produces a symptom complex that in some respects mimics the common cold also provides support for the hypothesis that IL-8 may contribute to common cold symptoms (Douglass et al., 1994).

The mechanism by which rhinovirus challenge stimulates elaboration of IL-8 has been examined at the cellular level in an attempt to identify potential targets for the interruption of this process. Although transcriptional activation of the gene for IL-8 is somewhat different in different cell lines, the need for activation of NF-κB appears to be consistent (reviewed in Mukaida et al., 1994). Recent data suggest that the IL-8 elaboration induced by RSV, influenza and rhinovirus is also mediated by NF-κB (Fiedler et al., 1995; Mastronarde et al., 1995, 1996; Zhu et al., 1997; Biagioli et al., 1998; Knobil et al., 1998). A single report has suggested that NF-κB may not be essential for the transcription of IL-8 following rhinovirus infection (Kim et al., 2000).

Reactive oxygen species in general and hydrogen peroxide in particular have been recognized as important mediators of the activation of NF-κB (Schreck et al., 1991). Many of the inducers of NF-κB are known to increase cellular production of hydrogen peroxide and NF-κB activation is diminished in cell lines that overexpress catalase (Schmidt et al., 1995). The role of oxidant stress in virus-induced NF-κB activation and IL-8 elaboration has been examined. Rhinovirus, influenza virus and respiratory syncytial virus-induced IL-8 elaboration is mediated by oxidant stress (Mastronarde et al., 1995; Biagioli et al., 1998; Knobil et al., 1998). These studies have also shown that treatment with antioxidants inhibits the IL-8 elaboration in response to challenge with these viruses.

The observations that virus-induced oxidative stress is an important trigger of the cellular response to a variety of viral pathogens led to studies to determine the mechanism by which this oxidative stress is produced. Oxidative stress may occur in a cell in response to a viral infection either by inhibition of normal antioxidant enzyme activities or by increased production of oxidants. Superoxide (O_2^-) in the cell is detoxified by the superoxide dismutases that catalyze conversion of superoxide to hydrogen peroxide which in turn is detoxified by catalase and glutathione peroxidase. The activities of superoxide dismutases, catalase, or glutathione peroxidase are not inhibited by virus infection (Kaul et al., 1997; Knobil et al., 1998) suggesting that oxidative stress is a result of increased production of pro-oxidants. Both reactive oxygen species (ROS) and reactive nitrogen species are pro-oxidants and an increase in either of these species would potentially result in cellular oxidative stress. Reactive nitrogen species are generated by the action of nitric oxide synthase on L-arginine to produce reactive nitric oxide. There are conflicting reports about the role of nitric oxide in rhinovirus infection or rhinovirus-induced IL-8 elaboration either in vitro or in vivo (Mastronarde et al., 1995; Sanders et al., 1998; Kaul et al., 1999). In contrast, it is clear that virus challenge results in increased concentrations of reactive oxygen species in the cell (Mastronarde et al., 1995; Biagioli et al., 1998; Knobil et al., 1998; Kaul, et al., 2000). These observations suggest that cellular oxidative stress in response to respiratory virus infection is due to an increased production of ROS.

A recent study reports evidence that NADPH-oxidase or a similar enzyme are the source of the increased superoxide in response to virus challenge. Oxidative stress, measured by nitroblue tetrazolium dye reduction or hydrogen peroxide production, was reduced following virus challenge of a fibroblast cell line deficient in p47-*phox*, one of the cytoplasmic components of NADPH-oxidase (Kaul et al., 2000). Similarly, treatment of a normal fibroblast cell line with an inhibitor of NADPH-oxidase prevented the IL-8 response to challenge with rhinovirus, RSV, or coronavirus. NADPH-oxidase homologues that participate in cellular signaling have been reported (Suh et al., 1999; Banfi et al., 2000). Of interest, rhinovirus stimulation of oxidative stress and IL-8 production by the cell does not appear to require viral attachment to ICAM-1 or virus replication (Schroth et al., 1999; Kaul et al., 2000).

2. Advances in symptomatic treatment of the common cold

Symptomatic therapy remains the only available treatment for the common cold. The usefulness of symptomatic therapies directed at specific symptoms of colds has been the subject of some controversy (Smith and Feldman, 1993). In spite of the questions about the efficacy of these products, they are widely used (Kogan et al., 1994; Simon and Weinkle, 1997; Kemper, 1998). Of interest, a small survey suggests that dietary supplements such as zinc and Echinacea are used as frequently as more conventional symptomatic treatments for the common cold (Kemper, 1998).

2.1. Zinc

The rationale for the use of zinc as a common cold treatment is not clear. The function of the rhinovirus 3C protease, an essential enzyme for rhinovirus replication (see protease inhibitors below), is inhibited by zinc (Korant et al., 1974; Cordingley et al., 1989). Although zinc has been found to inhibit rhinovirus replication in vitro there has been no evidence of an antiviral effect in vivo (Korant et al., 1974; Al-Nakib et al., 1987; Farr et al., 1987; Geist et al., 1987). It has also been suggested that interaction of zinc with host immune function might provide a beneficial effect on common cold symptoms (Macknin, 1999), however, a recent study found no detectable effect of zinc on nasal secretion IL-8 concentrations suggesting that the effects of zinc are not due to modulation of host responses (Turner and Cetnarowski, 2000).

The effect of zinc treatment on the duration or severity of common cold symptoms has been examined in at least 10 different studies since 1984 (Eby et al., 1984; Al-Nakib et al., 1987; Douglas et al., 1987; Farr et al., 1987; Smith et al., 1989; Weismann et al., 1990; Godfrey et al., 1992; Mossad et al., 1996; Macknin et al., 1998; Prasad et al., 2000). The results of these studies have been inconclusive. The studies that have found no effect of zinc have been criticized as having small sample sizes or for using inadequate doses of zinc or formulations of zinc that might inactivate the zinc salts. The studies reporting a significant effect of zinc have been criticized for inadequate blinding either by the use of poorly matched placebos or because the active preparation was associated with a high incidence of adverse effects. A recent study that was adequately blinded and used formulations of zinc that are generally accepted as appropriate found no effect of zinc treatment on natural colds and only a very modest effect on induced colds (Turner and Cetnarowski, 2000).

2.2. Echinacea

The genus Echinacea consists of nine species, three of which, *E. angustifolia*, *E. pallida* and *E. purpurea*, are used medicinally. Most medicinal preparations contain the expressed juice of *E. purpurea* aerial parts, or hydroalcoholic tinctures of *E. pallida* or *E. purpurea* roots. They are mainly used for nonspecific stimulation of the immune system and *E. purpurea* aerial parts and *E. pallida* roots are listed as approved herbs by the German Commission E as supportive therapy for colds and chronic infections of the respiratory tract (Blumenthal, 1998). In the United States, products are made from the roots, the whole plant or aerial parts of *E. pallida*, *E. angustifolia* or *E. purpurea*. These products are usually formulated as powdered plant material, alcoholic tinctures, tea preparations, or press juice of the flowers. Variations in the Echinacea species, plant parts, extraction procedures and manufacturing processes affect final product composition (chemical constituents or ratios of selected constituents) and may affect biologic activity. In spite of the considerable variation in Echinacea preparations, they have generally been used interchangeably in clinical studies.

The pharmacologic and chemical properties of Echinacea have been extensively reviewed by Bauer (Bauer, 1999). Much confusion still exists concerning the pharmacologic properties of this botanical due to inadequate standardization and the presence of contaminants in most preparations (e.g. presence of mixed Echinacea species and adulteration with *Parthenium integrifolium*). Constituents of Echinacea include the polar polysaccharides and glycoproteins, the moderately

polar caffeic acid derivatives and the lipophilic polyacetylenes and alkamides. The glycoproteins, polysaccharides, caffeic acid derivatives (cichoric acid) and alkamides have all been reported to have immunostimulatory activity (Stimpel et al., 1984; Bauer et al., 1989; Luettig et al., 1989). In contrast, the alkamides of *E. angustofolia* and *E. purpurea* exhibit antiinflammatory properties (Muller-Jakic et al., 1994). Thus, several substances found in Echinacea species could potentially affect common cold symptoms by modulation (either enhancement or suppression) of the host immune response (Stimpel et al., 1984; Cheminat et al., 1988; Bodinet and Buescher, 1991; Burger et al., 1997; See et al., 1997). The observation that echinacoside and cichoric acid are free radical scavengers and can protect against free radical induced injury (Facino et al., 1995) is also of interest in light of evidence that oxidative stress may play a role in virus-induced elaboration of IL-8 (Biagioli et al., 1998; Kaul et al., 2000).

The efficacy of Echinacea for the prevention or treatment of viral respiratory disease has been evaluated in several clinical trials. Studies of Echinacea as prophylaxis have generally found no effect (Melchart et al., 1994, 1998; Grimm and Muller, 1999; Turner et al., 2000). Positive results have been reported in clinical trials of Echinacea as treatment for colds. Early trials have been included in a previous review of this topic (Melchart et al., 1994). Three recent studies have also examined the effectiveness of Echinacea products given as treatment for the common cold. Brinkeborn et al. (1999) studied 199 patients who took Echinacea or placebo at the first sign of a cold. The Echinacea used in this study was a hydroalcoholic extract of *E. purpurea* aerial parts (95%) and roots (5%). A similar study was done in 120 volunteers using the squeezed sap of *E. purpurea* aerial parts (Hoheisel et al., 1997). Both of these studies reported significantly reduced severity of illness in volunteers treated with Echinacea. The results of these studies must be viewed with caution, however, since the efficacy analysis was based upon nonspecific evaluations of effectiveness (i.e. 'judged effective', 'progression of illness to a *real* cold') in volunteers who passively reported the occurrence of illness. A study

reported in 1999 used a more carefully standardized symptom scoring method and included active follow-up of enrolled patients (Henneicke-von Zepelin et al., 1999). Analyses that included the evaluation of 'general well-being' revealed a statistically significant benefit for the study drug, however, a significant effect on specific common cold symptoms was not observed. The study medication in this study included cedar leaf and indigo root in addition to the Echinacea and the effectiveness of the placebo blinding was not reported. The phytochemical profile of the Echinacea preparations was not reported in any of these previous studies.

2.3. Conventional symptomatic therapy

Conventional symptomatic treatments for the common cold have consistent but modest effects on specific cold symptoms. The first-generation antihistamines reduce rhinorrhea by 25–35% (Gwaltney et al., 1996; Gwaltney and Druce, 1997; Turner et al., 1997) and the topical anticholingeric, ipratropium bromide, has a similar effect (Duckhorn et al., 1992; Diamond et al., 1995; Hayden et al., 1996). The second generation or 'non-sedating' antihistamines have had no effect on common cold symptoms in a limited number of studies (Gaffey et al., 1988; Berkowitz and Tinkelman, 1991). This observation, the absence of histamine in the secretions of most subjects with colds (Eggleston et al., 1978, 1984; Naclerio et al., 1988; Igarashi et al., 1993), and the similarity of the response to ipratropium and the antihistamines suggest that the effect of the antihistamines on rhinorrhea is related to the anticholinergic rather than the antihistaminic properties of these drugs. The oral adrenergic agents reduce nasal obstruction by approximately 20% at the peak of activity (Dressler et al., 1977; Taverner et al., 1999) while the topical agents have greater activity (Akerlund et al., 1989). The modest therapeutic effect, bothersome side effects and symptom specificity of these treatments limits their utility.

An approach that examined the effect of combining symptomatic and antiviral compounds has also been reported. Gwaltney, reported effec-

tive treatment of established rhinovirus infections with a combination of naproxen, ipratropium bromide, and interferon-α2b (Gwaltney, 1992). The effect of this combination appeared to be greater than the effects usually seen with available common cold therapies.

2.4. Summary

Studies of the effect of treatment of dietary supplements such as Echinacea and zinc on common cold symptoms have produced inconsistent results and the benefit of these treatments remains unproven. Conventional symptomatic treatments have consistent but modest effects on specific cold symptoms. There is no evidence (or expectation) that these treatments will prevent the person-to-person spread of infection. Similarly, there is no evidence that symptomatic treatment will prevent the development of the complications of the common cold. Treatment of children with an oral antihistamine–decongestant combination did not prevent otitis media (Randall and Hendley, 1979). Similarly, the use of anticholinergic agents or oral or topical nasal decongestants has no effect on the eustachian tube dysfunction associated with the common cold (Doyle et al., 1993; Turner and Darden, 1996; Pitkaranta et al., 1998).

3. Progress in antiviral treatments for rhinovirus colds

3.1. Blockade of ICAM-1 receptor

The feasibility of receptor blockade was first suggested by the observation of Abraham and Colonno that many different rhinovirus serotypes shared the same cellular receptor (Abraham and Colonno, 1984). The major cellular receptor for rhinovirus was subsequently identified as intercellular adhesion molecule-1 (ICAM-1) (Greve et al., 1989; Staunton et al., 1989). A much smaller number of serotypes use cellular low-density lipoprotein (LDL) receptor as the site for virus attachment (Hofer et al., 1994). Subsequent studies showed that rhinovirus infection could be prevented in vitro by blocking access to the ICAM-1

receptor with monoclonal antibody (Colonno et al., 1986; Sperber and Hayden, 1989). Based on these observations, prophylaxis with intranasal monoclonal antibody to ICAM-1 was attempted by Hayden et al. (1988) in experimental colds in volunteers. In the most successful of these studies, a total of 1 mg/subject of anti-ICAM antibody was given over a period beginning 3 h before and ending 36 h after virus challenge. This treatment regimen reduced symptoms and viral shedding during the time the medication was being administered, however, when the medication was discontinued the amount of virus shedding increased and symptoms became more severe.

An alternative approach to receptor blockade was explored in studies using truncated forms of ICAM-1 created by deleting the transmembrane and intracellular domains of the protein. These molecules were shown to prevent infection with rhinovirus in vitro (Marlin et al., 1990; Greve et al., 1991). Later studies confirmed that these so-called soluble ICAMs prevented infection by a broad spectrum of rhinovirus serotypes in a variety of different cell lines (Crump et al., 1993; Ohlin et al., 1994). Soluble ICAM treatment was subsequently shown to prevent infection with rhinovirus type 16 in chimpanzees treated with 10 mg of sICAM administered intranasally zero to 10 min after rhinovirus challenge (Huguenel et al., 1997). A human clinical trial of sICAM using the experimental rhinovirus challenge model has also been reported (Turner et al., 1999). In this study sICAM was administered intranasally six time each day beginning either 7 h before or 12 h after rhinovirus challenge. Similar treatment effects were seen regardless of the timing of the treatment in relation to the viral challenge. Treatment with sICAM had no effect on the incidence of infection but did reduce symptoms. In an analysis that combined all treatment groups the frequency of clinical colds was reduced by 23%, the total symptom score was reduced by 45% and the total nasal secretion weight was reduced by 56% in the treated volunteers. There was also a significant decrease in the quantity of virus present in nasal secretions and an associated decrease in the concentration of interleukin-8 in nasal lavage fluid from treated volunteers. These results demon-

strate that a reduction in viral replication with an associated reduction in the host inflammatory response may have beneficial effects even after infection is established. While the results of this study are interesting, further study will be needed to determine whether treatment would be effective if started after the onset of symptoms and with a more practical dosing regimen.

The feasibility of receptor blockade for the minor receptor serotypes has also been demonstrated in studies done with soluble forms of the LDL receptor (Marlovits et al., 1998a,b,c). In this case, however, the soluble receptor appears to inhibit infection by causing aggregation of virus.

3.2. Capsid binding agents

The human rhinoviruses have an icosahedral structure formed by 60 protomers. Each protomer consists of four proteins designated VP1 –VP4. The structure of the rhinoviruses, resolved at the atomic level by crystallographic techniques, reveals a 'canyon' that surrounds the vertex of each protomer (Rossmann et al., 1985). This canyon forms the site of attachment for the cellular receptor for the virus (Olson et al., 1993). At the bottom of the canyon is a hydrophobic pocket formed by VP1 that is associated with a pore in the canyon floor that opens into a channel leading to the interior of the virus. This hydrophobic pocket is the binding site for the so-called capsid binding agents (Smith et al., 1986). The mechanism of the antiviral effect of these compounds is complex. Attachment of rhinovirus to the cellular receptor, subsequent movement of the virus into the host cell, and uncoating of the viral protein coat to release the infectious RNA are critical events in the initiation of rhinovirus infection that appear to be inhibited in different viral serotypes by these agents (Ninomiya et al., 1984; Fox et al., 1986; Pevear et al., 1989; Shepard et al., 1993). A large number of different molecules that bind to this hydrophobic pocket have been found to have antiviral activity, however, for a variety of reasons none of these compounds has been broadly effective in clinical studies (reviewed in Arruda and Hayden, 1995). More recently a modification of some of these earlier molecules has

resulted in a compound, pleconaril, that has favorable pharmacokinetics, is metabolically stable, and retains broad and potent antiviral activity (Diana et al., 1995).

Pleconaril has been evaluated in an a study of experimental enterovirus infections (Schiff and Sherwood, 2000). In this study, 33 volunteers were given pleconaril or placebo at 12 h intervals for 7 days. Two hours after the second dose of study medication all volunteers were challenged with coxsackievirus A21 by intranasal inoculation. The pleconaril-treated volunteers had a significant reduction in nasal mucus production and total respiratory symptom score compared to placebo-treated volunteers. Pleconaril appeared to delay viral shedding but had no effect on the overall rate of infection with the virus. Subsequent studies of pleconaril treatment of natural colds have been completed (Hayden et al., 1999), however, the results of these studies have not yet been published.

3.3. 3C protease inhibitors

The rhinovirus genome encodes a single large polyprotein that is cleaved to produce the individual structural and enzymatic proteins of the virus. The 3C protease participates in many of these cleavage reactions. The importance of this protease to rhinovirus replication and the fact the active site of the protease appears to be highly conserved in all rhinovirus serotypes suggested that this enzyme was a potential target for antiviral therapies. Efforts to design inhibitors of this enzyme have resulted in development of a 3C protease inhibitor, designated AG7088, that has recently been advanced to human clinical trials (Matthews et al., 1999). Studies of this molecule in vitro revealed potent activity for a broad spectrum of rhinovirus serotypes that was seen even when the drug was added to cells several hours after virus infection (Patick et al., 1999). This inhibition of virus replication was associated with a concomitant inhibition of virus-induced cytokine elaboration (Zalman et al., 2000). On the basis of these studies, clinical trials of AG7088 have been conducted both in experimental human rhinovirus infections and in natural colds. The

results of these studies have not yet been published.

3.4. Summary

Preliminary reports that these antiviral compounds may have treatment effects even when given after onset of illness suggest that these new efforts at antiviral treatment of rhinovirus colds represent a substantial advance over previous efforts. Prior to the reports on soluble ICAM, no antiviral therapy had produced an impact on common cold symptoms when given after infection of the nasal mucosa was established. In spite of these promising results, the requirement that an antiviral drug not only inhibit virus replication but also be associated with a clinically significant effect on symptoms poses a formidable barrier to these agents. For rhinovirus colds, the time from the first detectable symptoms to the peak symptom severity is generally only 24–36 h. Thus, the beneficial effect of antiviral treatment must generally be detectable against a background of resolving illness. A second obstacle to the development of antiviral treatments for the common cold is the fact that these antiviral agents are virus-specific while many different viruses have been associated with the common cold syndrome. In contrast to the influenza viruses that produce a relatively distinct clinical syndrome, the diagnosis of a rhinovirus infection on the basis of the clinical syndrome is likely to be inaccurate. This inability to accurately diagnose these infections clinically suggests that effective use of an antiviral treatment will likely require the simultaneous availability of a point-of-use diagnostic assay for rhinovirus. Attempts to develop such an assay have been unsuccessful to date. The development of useful antiviral agents for the common cold is further complicated by the potential cost of this therapy. In the United States, a newly approved antiviral therapy will almost certainly be given under physician supervision which will add both cost and logistical barriers to the use of the drug. Finally, the generally benign and self-limited natural history of the common cold mandate that any agent used for treatment of this condition have minimal toxicity or side effects. It remains to

be determined whether these new antiviral agents will surmount these barriers.

An additional consideration for the use antiviral treatments for rhinovirus infections is the potential for development of antiviral resistance. Resistance to soluble ICAM develops readily in vitro (Arruda et al., 1994). Naturally occurring resistance to the capsid binding agents has also been documented (Heinz et al., 1989; Groarke and Pevear, 1999). Studies in vivo, however, suggest that picornaviruses resistant to the capsid binding agents may have reduced virulence (Yasin et al., 1990; Groarke and Pevear, 1999). No mutants resistant to the 3C protease inhibitors have been reported in the limited experience with these agents.

4. Potential new targets for treatment

In spite of repeated attempts over many years the effort to produce highly effective treatments for the common cold has to date been unsuccessful. These efforts have focused primarily on either inhibition of viral replication or direct antagonism of the end symptoms. The observation that a variety of different viral respiratory pathogens cause oxidative stress in the cell and the elucidation of the signal transduction events triggered by this oxidative stress may produce potential new targets for treatment of illnesses caused by these agents. Although treatment with antioxidants to prevent respiratory disease has been reported (De Flora et al., 1997), a systematic study of antioxidant treatments for the common cold have not been published. The apparent role of NF-κB activation in the host response presents another potential target for treatment. Corticosteriods appear to inhibit rhinovirus-induced NF-κB activation in vitro (Papi et al., 2000) and kinin production following rhinovirus infection in vivo (Farr et al., 1990; Gustafson et al., 1996), however, steroid treatment increases virus replication and has no effect on common cold symptoms (Farr et al., 1990; Gustafson et al., 1996; Puhakka et al., 1998). Identification of additional events in the signal transduction pathways that produce the cellular responses to these viral pathogens will

provide additional opportunities to interrupt these pathways and modify the host response to the infection. Finally, if individual mediators are found to play a predominant role in the pathogenesis of symptoms, specific inhibitors of these mediators (e.g. anti-IL-8 antibody) may have a beneficial impact on illness.

Many questions remain to be answered before the usefulness of this approach can be determined. As with the antiviral agents, inhibition of the inflammatory response once symptoms have already occurred may be associated with a limited effect on the resolution of the illness. It is also not clear whether host responses that are unwanted and associated with symptom production can be targeted without interfering with host responses that are necessary for resolution of the illness. Finally, a major impetus for the treatment of the common cold is prevention of the complications of otitis media, sinusitis, and exacerbations of asthma that are the major source of morbidity associated with this infection. Approaches to this illness, whether antiviral or antiinflammatory, that do not impact these complications will have limited utility.

5. Summary

The common cold is an important illness both as a result of the economic impact of this common disease and because of the morbidity associated with the complications of the illness. Recent attempts to develop antiviral treatments for the common cold represent a substantial advance over previous efforts. Formidable barriers remain to be overcome, however, before any of these new products will be proven to be clinically useful. Recent advances in our understanding of the pathogenesis of common cold symptoms have provided insights into potential new targets for the treatment of this illness.

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