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Efficacy of fusafungine in acute rhinopharyngitis: a pooled analysis*

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SUMMARY

Upper respiratory tract infections are generally mild but they are associated with an enormous loss in productivity. Treatment consists of reduction of local symptoms e.g. local inflammation and prevention of potential superinfections. Besides its bacteriostatic activity against most micro-organisms involved in respiratory tract infections fusafungine displays original anti-inflammatory properties.

To optimise nasal and throat deposition, a new fusafungine oro-nasal spray using HFA 134a was developed and its efficacy was evaluated in patients with acute rhinopharyngitis based on improvement of significant nasal symptoms. Three randomised double-blind placebo-controlled parallel-group studies with identical objectives design and dosage were performed and results were pooled for a better evaluation of treatment effect (532 patients).

The percentage of responders (patients with nasal symptom score improvement from Day 0 to Day 4) was 61.5 ± 2.9% with fusafungine vs 46.8 ± 3.1% with placebo (p=0.009) with an odds ratio of 1.8 (p=0.01) in favour of fusafungine. The nasal symptom score distribution at Day 4 showed an odds ratio of 1.56 (p=0.011) also in favour of fusafungine. For patients treated early (onset of symptoms £1 day) the percentage of responders was 65.9 ± 4.1% with fusafungine vs 38.3 ± 4.0% with placebo (p=0.022) with an odds ratio of 3.08 (p=0.033) in favour of fusafungine.

Therefore fusafungine through its dual bacteriostatic and original anti-inflammatory properties is an effective treatment of acute rhinopharyngitis especially when administered early.

Key words: fusafungine; rhinopharyngitis; nasal symptom score.

INTRODUCTION

Upper respiratory tract infections (URTIs), which represent one of the most frequent infectious diseases in man are generally mild and self-limiting but they account for a big economic burden due to an important loss in productivity (several million days of school absence and work annually and high medical costs) (Turner, 1997). Although URTIs are mainly of viral origin, a bacterial infection may follow the initial infection favoured by epithelial cell damage which increases bacterial adherence (Kaiser et al., 1996). The presence and multiplication of these micro-organisms maintain continuous mucosal damage and lead to an inflammatory vicious circle responsible for clinical symptoms characterised by rhinorrhoea, nasal congestion, sneezing, and a sore throat sometimes accompanied by fever and malaise. Moreover these micro-organisms may produce complications like otitis media, acute sinusitis or even pneumonia.

There is no specific therapy and the main treatment goals consist of improvement in the illness symptoms essentially by reducing local inflammation and preventing potential superinfections. Currently available treatments are generally limited to symptomatic therapies with time-limited efficacy and potential side effects (Turner, 2001; Heikkinen and Jarvinen, 2003). More specific antiviral treatments are available, but they have limited clinical efficacy and may have important adverse effects (Turner, 2001). Physicians and patients are often concerned by the possibilities of complications, particularly superinfections with the result that systemic antibiotics tend to be inappropriately prescribed alongside drugs for purely symptomatic relief (Gonzales et al., 2001; Turner, 2001). This runs against recommendations for medical practice and contributes to changes in the microbial ecology with the generation of resistance to antibiotics. Furthermore this practice leads to unjustified increases in health costs.

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Fusafungine, which is extracted from the mycelium of *Fusarium lateritium* displays bacteriostatic activity against most micro-organisms responsible for both infections and superinfections of the respiratory tract including *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis* (German-Fattal, 1994). It has anti-adherence activity against *Haemophilus influenzae* another important micro-organism involved in superinfections (German-Fattal, 1989). By reducing the multiplication and spread of bacteria whose presence maintains continuous mucosal damage, fusafungine can participate in the reduction of local inflammatory reaction and consequently the most bothersome symptoms of URTI. In addition direct anti-inflammatory effects of fusafungine were observed in experimentally induced inflammatory disorders in animal models, while the mechanisms of the anti-inflammatory activity of fusafungine were investigated at the cellular and molecular levels (Jousserandot et al., 1981; Gosset et al., 1996).

In order to optimise the aerosolisation of fusafungine allowing a well-distributed nasal and throat deposition and to promote local action with a pressurised formulation, a new oro-nasal spray using HFA 134a as a propellant gas was developed. This newly developed fusafungine formulation was evaluated in patients with acute rhinopharyngitis. Efficacy assessment was based on reduction of bothersome symptoms in these pathologies. Three double-blind, placebo-controlled, randomised studies were performed one with French general practitioners, the second in a common cold centre in the UK; and the third with a site management organisation (SMO) in Netherlands. As these studies were homogeneous in terms of patient population, study design, treatment dose, and assessment criteria, a pooled analysis was performed for a better evaluation of efficacy.

MATERIAL AND METHODS

Patients

Patients were recruited by advertisement with compensation for participation (studies performed in the UK and The Netherlands) or by general practitioners (study performed in France). Callers were screened by telephone and were invited to meet with a physician if eligible, usually within a few hours of the initial call.

At the enrolment interview, the physician obtained informed consent and gathered baseline data. Inclusion criteria were as follows: 1) male or female outpatients, aged 18 years and over, who had given their written informed consent; 2) patients with non-complicated acute infectious rhinopharyngitis within 3 days of the onset of the symptoms (rhinopharyngitis was diagnosed on both nasal symptoms [nasal secretion and/or nasal obstruction] and pharyngeal symptoms [dysphagia and/or sore throat]); 3) patients not receiving or not having received any systemic or upper respiratory tract topical antibiotic or anti-inflammatory therapy within the 5 days prior to inclusion. Patients were not included when suffering from rhinopharyngitis with clinical signs of superinfection: purulent nasal discharge, temperature greater than 38.5°C, and/or systemic symptoms.

Study medication

The active treatment in these studies was the new formulation of fusafungine. Placebo and active treatments were presented in identical canisters (10 mL oronasal spray) so as to maintain the blinding of the study. In addition to obtain a placebo oronasal spray with taste, odour, and viscosity as close as possible to the active one, the same excipients were introduced at the same concentration in both the active and placebo canisters. Fusafungine or placebo was to be administered 4 times a day, at 4-hour intervals during waking hours, for 7 days (from D0 at inclusion visit to D7 before end of study visit). Each application consisted of administration of 8 puffs: 4 puffs in the throat and 2 puffs in each nostril corresponding to a daily administration of 4 mg fusafungine. Subjects were randomly assigned to receive either fusafungine or placebo at the time of enrolment into each study in chronological order of inclusion. Active and placebo oronasal sprays were manufactured according to good manufacturing practice (GMP). The patients were asked to return the canisters at the D4 and D7 visits. Each canister was individually weighed before use (at the end of the manufacturing process) and after use (at the end of the study). Compliance was calculated as weight of solution used (g) / theoretical weight of solution to be used (g). The theoretical weight of solution to be used was estimated as: number of treatment days, 4 applications/day, 8 puffs/application, 0.033 (mean weight of one puff).

Study design

The three individual studies were designed as randomised, double-blind, placebo-controlled, and parallel-group studies. They were conducted under strict data monitoring and data collection in compliance with national regulations in the study countries regarding ethics, patient information, and relationship with investigators and in compliance with good clinical practice (GCP). The first study was a French multicentre study conducted by general practitioners (from February to April 1999); the second was conducted in a specialised common-cold centre in the UK (from February to June 1999); and the third in 7 centres of a SMO in The Netherlands (from January to May 2002). The study design comprised 3 visits at D0, D4, and D7. There was no run-in period. Selection, inclusion, and randomisation took place at D0. Treatment was initiated at D0 during inclusion visit and ended at D7 before end study visit, resulting in a 7-day treatment period.

Evaluation of illness severity

Illness severity was assessed using a method derived from that proposed by Jackson et al. to describe the evolution of a common cold (Jackson et al., 1958). Each morning, patients self–assessed 2 nasal scores “runny nose” and “nasal obstruction” and reported it in a diary using a 4-point ordinal scale from 0

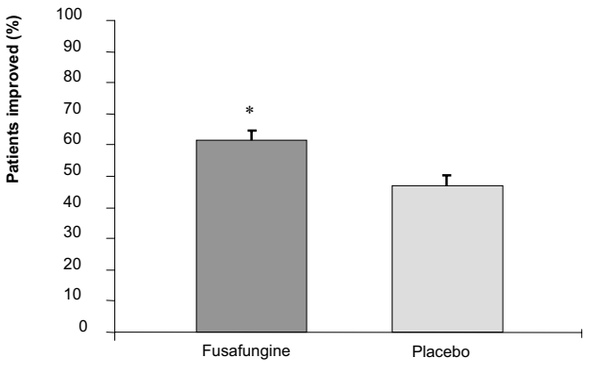

Figure 1. Responder rates (percentage of patients with improvement of nasal symptom scores from D0 to D4) in the three studies. * p=0.009.

to 3 ("not at all", "slightly bothersome," "moderately bothersome," or "very troublesome"). The main judgment criterion was total nasal score (sum of scores for "runny nose" and "nasal obstruction"), classified in three classes: absent or minor (0-1), moderate (2-4), or severe (5-6). Assessment of efficacy was based on total nasal symptom score change from D0 baseline to D4 ("improved" i.e., change to a lower class versus "stable or aggravated" same class or higher) and on its value (distribution by class) at D4.

Safety evaluation

A complete physical examination was performed at each visit. Any sign or symptom– regardless of its nature, severity, seriousness, and the presumed causal role played by the product or the experimental procedure– presented or spontaneously reported by the patient was recorded in the case report form.

Statistics

On the basis of initial results, each study was designed to have 100 patients in each group, providing at least 80% power to detect a difference in improvement of nasal symptoms.

To be legitimate, the pooled analysis should result in formulation of an estimate overall average effect based on individual effects of treatment estimated in the three trials. First, we evaluated the study-specific effects of treatment separately in the different trials and the homogeneity of the treatment effect according to the three trials. The effect of treatment based on the binary response categorised in two classes "improved" versus "unchanged or worse" and was expressed on two different scales:

- The proportion of success (improved patients) in the two groups.
- The odds scale, the treatment effects will be expressed as the odds ratio. Odds will always be expressed as the ratio of the proportion of success, "improved" divided by the proportion of failures "unchanged or worse."

The ordinal response categorised in three classes after 4 days of treatment (last value from D1 to D4) was only expressed in odds ratio of success adjusted for baseline levels and treatment.

Since the treatment effect turned out to be larger in the smallest study (the UK) than in the larger ones (France and The Netherlands), an overall treatment effect was estimated taking into account treatment-effect heterogeneity. The method chosen is contained in Whitehead, 1991.

A two-tailed 95% confidence interval was calculated for the true overall treatment effect.

Due to the fact that in two studies (France and the UK), treatment effect was shown to be influenced by an early treatment initiation, a pooled analysis on all trials was conducted to estimate efficacy in patients with a duration of rhinopharyngitis £1 day.

RESULTS

Efficacy

A total of 566 patients were randomised in the three studies and the 532 patients who had at least one evaluation of the main criterion under treatment (255 in the fusafungine group and 277 in the placebo group) were included in the pooled analysis (full analysis set). The demographics and the baseline nasal symptom score distribution by class were similar in the treatment groups and are described for each study in the Table 1. In the UK, due to delay in recruitment before the beginning of the pollen season with increasing numbers of allergic rhinitis, only 72 patients could be included.

Compliance assessment based on weighing the canisters before and after the treatment period was very good for the three studies and are described in the Table 1.

The percentage of responders (patients with nasal symptom score improvement from Day 0 to Day 4) was 61.5 ± 2.9% with fusafungine vs 46.8 ± 3.1% with placebo (p=0.009) (Figure 1) with an odds ratio of 1.8 (p=0.01) in favour

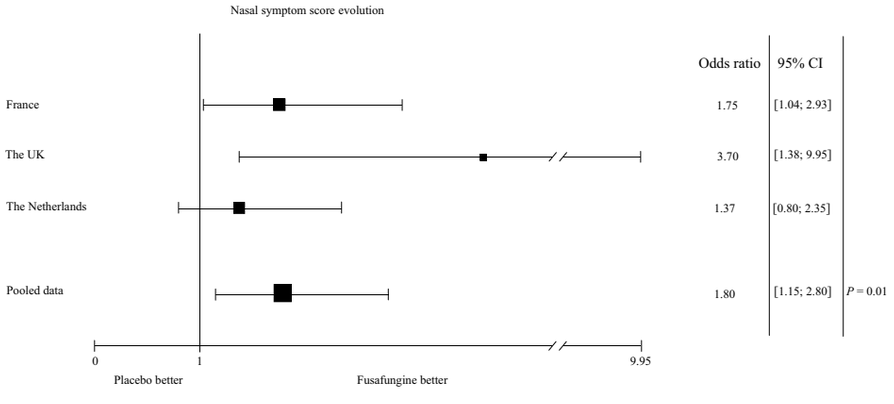

Figure 2. Odds ratios for the nasal symptom score evolution in the three individual studies and in the pooled analysis. The area of the square representing the point estimate is proportional to the number of patients in the study. CI, confidence interval.

Table 1. Demographic characteristics of participants, compliance and duration of symptoms in the three individual studies.

		Randomised Set	Age mean * SD (years)	Sex M / F	Full analysis set	Nasal symptoms Distribution by class at baseline minor / moderate / severe	Compliance (mean*SD)	Duration of rhinopharyngitis *1 day before inclusion
France	Placebo	127	37.9*14.8	48 (38%) / 79 (62%)	118	11 (9%) / 75 (64%) / 32 (27%)	90.1*40.2 %	61 (52%)
	Fusafungine	139	37.5*12.4	52 (37%) / 87 (63%)	129	10 (8%) / 74 (57%) / 45 (35%)	92.3*42.1 %	73 (57%)
The UK	Placebo	36	20.6*2.8	12 (33%) / 24 (67%)	34	4 (12%) / 23 (68%) / 7 (20%)	92.1*38.7 %	17 (50%)
	Fusafungine	36	21.1*2.1	10 (28%) / 26 (72%)	36	4 (11%) / 20 (56%) / 12 (33%)	85.4*31.1 %	18 (50%)
The Netherlands	Placebo	111	27.2*11.3	25 (22%) / 86 (78 %)	103	13 (13%) / 58 (56%) / 32 (31%)	102.2*18.8 %	74 (72%)
	Fusafungine	117	28.7*11	26 (22%) / 91 (78%)	112	5 (4%) / 71 (63%) / 36 (33%)	103.3*24.9 %	66 (59%)

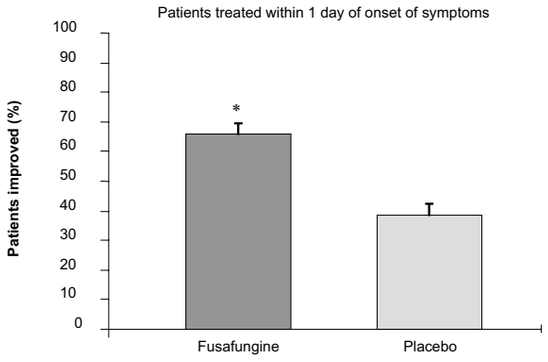

Figure 3. Responder rates (percentage of patients with improvement of nasal symptom scores from D0 to D4) in patients of the three studies treated early (within 1 day of onset of symptoms). * P=0.022.

of fusafungine (Figure 2). The nasal symptom score distribution at Day 4 showed an odds ratio of 1.56 (p=0.011, confidence interval [1.10-2.20]) also in favour of fusafungine. For patients treated early (onset of symptoms 1 day, 157 patients in the fusafungine group and 152 patients in the placebo group) the percentage of responders was 65.9 ± 4.1% with fusafungine vs 38.3 ± 4.0% with placebo (p=0.022) (Figure 3) with an odds ratio of 3.08 (p=0.033) in favour of fusafungine (Figure 4).

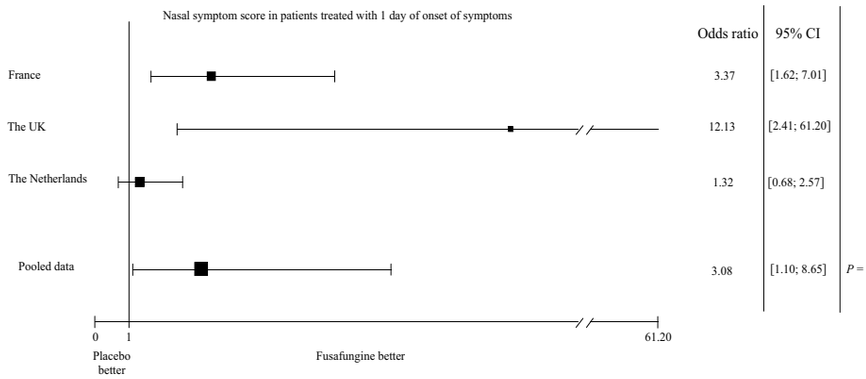

Figure 4. Odds ratios of the nasal symptom score evolution in the three individual studies and of the pooled analysis for patients treated early (within 1 day of onset of symptoms). The area of the square representing the point estimate is proportional to the number of patients in the study. CI, confidence interval.

At D7 there was no significant difference in nasal symptom score between fusafungine and placebo group.

Safety and tolerability

All subjects who received treatment were included in the analysis of the safety and tolerability of fusafungine. Overall fusafungine was well tolerated. The percentage of patients who experienced one or more adverse events was similar in both groups: 30% in the fusafungine group and 24% in the placebo group (not statistically different). The most frequently reported events were linked to the study disease (respiratory disorders) or local tolerance (headache, application site reaction). Among the patients only 5 (1.7%) patients in the fusafungine group and 9 (3.2%) in the placebo group withdrew from the treatment due to adverse events.

DISCUSSION

The pooled analysis of these three studies conducted in compliance with GCP showed that 61.5% of patients were improved with fusafungine compared with 46.8% with placebo. The efficacy of fusafungine was greater with early treatment as the percentage of responders was 65.9% with fusafungine vs 38.3% with placebo when patients were included within 1 day of onset of symptoms. These results are confirmed by an odds ratio of improvement of 1.8 for all patients and 3.08 for patients included within 1 day of onset of symptoms in favour of fusafungine.

Rhinopharyngitis is one of the most common URTIs and represents a good model to evaluate efficacy of a topical treatment. In order to adhere closely to medical practice, the clinical efficacy of fusafungine was assessed on the improvement of the bothersome nasal symptoms associated with URTI (runny and blocked nose) rather than on microbiological evaluation. Microbiological assessments are not considered relevant in these studies since the upper respiratory tract is not sterile and the bacterial responsibility would be difficult to document given

the presence of pathogens not related to the URTI. The identification of pathogens by microbiological culture likely to be responsible for the development of an infection would lead to overtreatment with systemic antibiotics (Mainous, 1996). In addition in clinical practice, there is no diagnostic test rapid enough to guide the choice of treatment which is mainly driven by clinical symptoms. In such pathologies, relief of bothersome clinical symptoms represents the main therapeutic demand of patients.

In order to describe the evolution of the common cold, Jackson et al. developed an objective and consistent method of scoring symptoms. Eight symptoms related to the nose and throat regions or general welfare were scored from 0 to 3 according to their absence or presence to a mild, moderate or severe degree (Jackson et al., 1958). The best way to appreciate the symptom score is an independent self-evaluation by the patient. Evaluation by the investigator is only complementary. Thus clinical trials on drug efficacy are generally based on the evolution of self-evaluated symptomatic scores. In order to assess the efficacy of fusafungine a topical treatment in the nose and the throat, only local symptomatic scores reflecting local inflammation of nose or throat were evaluated. Nasal symptom scores are the most troublesome in rhinopharyngitis and their evolution from D0 to D4 were chosen as the main criteria, since a sore throat generally resolves spontaneously within the first days of the URTI.

In accordance with GCP, fusafungine studies were placebo-controlled since there is no reference therapy in URTI. Since the active ingredient is fusafungine, only fusafungine was removed from the placebo. However, it should be noted that the complete manufactured product contains menthol as an excipient which was maintained in the placebo in order to fully respect the blinding process. Menthol may provide some relief from nasal symptoms, especially by providing relief from nasal congestion, and the presence of menthol in both the active and placebo treatments may have reduced the relative magnitude of the reduction in symptom scores caused by fusafungine (Eccles, 1994).

The total number of subjects included in each study is comparable to studies performed to investigate drug efficacy in similar pathologies (Gwaltney and Druce, 1997). Similarly, the number of patients included in this pooled analysis is comparable to other meta-analysis performed for these conditions e.g. a meta-analysis was performed on the use of zinc salt lozenge use in the common cold in 6 studies comprising a total of 540 patients (Prasad et al., 2000).

The natural history of symptom scores in the common cold has been precisely described by Jackson et al. who showed their bell-shaped evolution and their natural decrease from D6 (Jackson et al., 1958). Nasal obstruction and an increase in nasal secretion both reflect local inflammation. Once the epithelium is invaded and viral replication has started, inflammatory and immune responses are evoked by the host. The observed migration of immune effector cells and their subsequent activation is orchestrated by mediator and cytokine release which results in a cascade of inflammatory reactions resulting in vasodilatation and increased vascular permeability responsible for URTI symptoms. Studies in naturally acquired respiratory tract infections have shown an increase in concentration levels of interleukins (IL) IL-1ß, IL-6, and IL-8, tumor necrosis factor a (TNF-α), MPO and elastase in nasal lavage fluid of symptomatic subjects compared to baseline values. Moreover a direct relation has been found between the increase in IL-1ß, IL-6, IL-8, and MPO in nasal fluid and the severity of URTI symptoms (Van Kempen et al., 1999).

The clinical efficacy of fusafungine may be due to the anti-inflammatory properties of fusafungine consistent with its observed in vitro effects on the release of cytokines which are known to be involved in URTI symptoms (German-Fattal, 2001). Thus direct anti-inflammatory effects of fusafungine were observed in experimentally induced inflammatory disorders in animal models and the mechanisms of the anti-inflammatory activity of fusafungine have been investigated at the cellular and molecular levels (Jousserandot et al., 1981; Gosset et al., 1996; Otori et al., 1998). Fusafungine reduces the TNF-α, IL1-ß, IL-6, and IL-8 release by human alveolar macrophages isolated from broncho-alveolar lavage liquids (BALs). Finally after 24 h of culture with macrophages, fusafungine was shown to down regulate the expression of ICAM-1 (intercellular adhesion receptor molecule-1), a receptor involved in virus adhesion, the initial step for virus replication (German-Fattal, 2001).

The efficacy of this new form of fusafungine is in accordance with the efficacy of the previous pressurised formulation of fusafungine in various URTIs (Abruzzi and Cohen, 1968; Feutren, 1980; Cuenant, 1988; Reinert, 1989; Hamann, 1994; Samolinski et al., 1997; Pandraud, 2002). The previous pressurised formulations used CFC and under the Montreal Protocol CFCs were to be phased out worldwide. A new propellant, the hydrofluoroalkane norflurane (HFA 134a) was identified to replace CFCs. HFA 134a was tested and proven to be safe and reliable, delivering reproducible and precise doses (Alexander, 1995a; Alexander and Libretto, 1995b). It is largely used as a propellant gas in several metered dose inhalers (MDIs).

The increase in efficacy demonstrated when fusafungine was given at an early stage of the URTI is consistent with what was observed with other treatments. It may be related to the interruption of the cascade of inflammatory mediator release and to a limitation in the multiplication of bacteria.

Physicians and patients are often concerned about the possibility of upper respiratory tract complications, particularly bacterial superinfection with the result that systemic antibiotics tend to be inappropriately prescribed alongside drugs for purely symptomatic relief (Kaiser et al., 1996; Gonzales, 2001). This runs against recommendations for medical practice and contributes to changes in the microbial ecology with the generation of resistance. Furthermore this practice leads to unjustified

increases in health costs. As a topical antimicrobial agent, fusafungine has the advantage of being able to act directly at the site of infection and provide high local drug concentration with minimal systemic absorption and fewer adverse effects than those likely to occur with systemic antibiotics administration.

The benefits of fusafungine resulting from its bacteriostatic and anti-inflammatory properties were analysed in the context of its prescription in general practice. A 1-year retrospective survey conducted in France on 30.500 patients with rhinopharyngitis clearly demonstrated that early administration of fusafungine contributes to a reduction in the prescription of systemic antibiotics and anti-inflammatory drugs including corticosteroids with a reduction in prescription costs consistent with current recommendations (Laccourreye et al., 2002; Fagnani and German-Fattal, 2003).

The current pooled analysis of three randomised, double-blind, placebo-controlled and parallel group studies confirms that fusafungine is effective in relieving bothersome nasal symptoms in rhinopharyngitis, especially when administered early.

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