A Pilot Clinical Trial to Evaluate the Efficacy of a Topical Antiviral Osmotically Active Hypertonic Solution for the Treatment of Influenza Virus Induced Sore Throat

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Abstract

Objectives: The presence of free virus particles and bacteria on the surface of the throat is the main cause of initiating and maintaining viral throat infection. In the absence of any topical antiviral treatment, the objectives of this study were to evaluate the efficacy and safety of some specific virus glycoprotein neutralizing and proteolytic enzyme binding plant tannins in an osmotically active hypertonic solution (VB-Th4) for the treatment of sore throat.

Methods: 60-patients having acute sore throat were treated with VB-Th4 spray for a maximum period of 14-consecutive days. 43 patients in the Standard treatment (ST) group received other commonly used treatments. Effect on clinical signs, duration of recovery and requirement for the use of antibiotics was evaluated.

Results: VB-Th4 significantly reduced the signs of sore throat, bacterial load as well as throat pain, irritation and inflammation immediately after the first treatment with complete recovery in 90% patients within 7-days. The time required for complete recovery and the use of antibiotics was significantly reduced in the VB-Th4 compared to the ST group.

Conclusion: In the absence of any topical antiviral drug, topical virus glycoprotein and protease inhibitors open a new therapeutic approach to treat throat viral infections.

Keywords: Influenza virus; Sore throat; Proteases; Glycoproteins; Procyanidins

Introduction

Throat viral infections, particularly the influenza and parainfluenza virus inducing upper respiratory tract infections, are very common in human beings [1].

Initially only a few virus particles come in contact with the throat mucous membrane, enter into the cells, multiply and millions of new virus particles are then liberated topically on the throat surface. These free virus particles now attack new healthy cells and weakens local immunity which is followed by secondary bacterial infection leading to pain, irritation, inflammation, fever and other signs of flu.

Influenza is an enveloped virus with a complex viral coat containing several glycoproteins (Gps). Virus envelop Gps are transmembrane proteins, anchored to the envelope by a hydrophobic domain. Virus uses these glycoproteins to attach to the cell membrane and to enter into the host cell [2]. The differences in the surface Gp structures confer different morphology and antigenicity in the same family of virus [3]. Continuous discovery of new virus surface Gps, their role in host cell infection and frequent viral mutations makes the development of a specific topical antiviral drug nearly impossible. In addition to the virus surface glycoproteins, topically liberated proteases on the throat surface also play an important role in facilitating influenza virus entry into the cell [4,5].

In the absence of any specific antiviral drug, vaccines are currently considered the best antiviral therapy but requires continuous adaptation due to regular changes in virus surface Gps. This is the reason why almost all the currently available antiviral drugs are directed to interfere with intracellular virus multiplication process but have no effect at all on free virus particles present on the throat surface, which is the main cause of throat infections.

Taking into consideration the protein nature of the proteases and the virus Gps on one hand and the protein binding properties of certain plant tannins, the aim of our research was to identify all the Gs and the proteases involved in the influenza virus infection and to search corresponding tannins or the procyanidin (PCD) fraction of the tannin having a strong capacity to bind with these proteins so as to stop topical viral growth.

Tannins are abundant in the plant kingdom and are known to bind with a wide range of protein molecules [6]. The procyanidin (PCD) fraction of the tannins contains big phenolic compounds with multiple structure units and may have selective protein binding properties [7]. This multiple structures of tannins confer them the possibilities to form strong permanent hydrogen bonds with a group of proteins. We analyzed the protein binding capacity of above 300 different PCDs by incubating PCDs with virus suspension or proteases followed by evaluating virus titre in influenza virus sensitive MDCK (Madin –Darby Bovine Kidney) cells as described by Shrivastava [8]. The selected plants PCDs were then added in a hypertonic osmotically active solution [9] as a cleaning agent on the throat surface to evacuate the bounded protein-PCD complexes from the throat surface. After initial selection of the best antiviral composition, a pilot clinical trial was conducted to verify clinical efficacy of the preparation, coded as VB-Th4 in patients suffering from acute viral sore throat. A parallel group of patients receiving other commonly used treatments was incorporated in the trial.
study as a Standard Treatment (ST) group to evaluate the duration of complete recovery and the use of antibiotics, if any, in the two groups.

Materials and Methods

Test product preparation

More than 300 different PCDs from 128 tannin rich known plants were prepared using the method described by B. Giner-Chavez et al [10]. In short, initial tannin rich plant extract was obtained with an aqueous organic solvent containing 70% acetone and 30% water. The extracts were then successively passed through Sephadex LH-20 columns by progressively increasing the volume of methanol (60 x 88.5 cm) and the intended fractions were eluted to produce a dry solid. The product was identified by mass spectrometry. The extracts mainly contained procyanidin (epicatechin –catechin) B1, B2, B3 and C1 fractions between 60-80% depending upon the part of the plant used.

The proteases involved in enhancing influenza virus entry into the cells, virus surface glycoproteins, and specific PCDs capable to bind with one or more of these proteins were evaluated employing the methods as described previously [8]. In short, to identify the proteases, influenza virus sensitive MDCK cells were grown in 96-well tissue culture plates (Corning, USA) in vitro in a protease free Dulbecco’s Modified Eagle’s Medium (DMEM). Cells were infected with a multiple Gp expressing human parainfluenza virus type 1 (ATCC-US, Ref: VR 94, Strain C35) adapted for tissue culture, to culture 50 and 100% tissue culture infective doses (TCID$_{50}$,TCID$_{100}$). Proteases were then added into the culture medium, either individually or in association, to evaluate the effect on virus growth. Increase in virus growth indicated participation of the protease(s) to enhance viral infection. To evaluate virus protein binding properties of PCDs, a fixed concentration of virus (TCID$_{50}$) and/or proteases were pre-incubated with a specific PCD, and the reduction in virus growth was evaluated compared to the corresponding controls. Low virus growth indicated virus or protease neutralization with the PCD. All active PCDs were then associated in varying concentrations so as to obtain 100% inhibition of virus infection in vitro. The concentration of each PCD required to inactivate 100% virus growth in a single well (surface area 0.328 cm$^2$) of 96-well culture plate was determined and the final association was designated as VB-Th4-PCDs. The PCD association (0.78%) was incorporated in a osmotically active hypertonic solution [11] containing glycerol (74.27%), honey (12.0%), and water (12.95%) so as to apply between an osmotically active hypertonic solution [11] containing glycerol (74.27%), honey (12.0%), and water (12.95%) so as to apply between

Clinical trial

Location: An open, label, prospective, multicentric, pilot study was conducted by the Nexus Clinical Research Pvt Ltd at Mumbai in India between 07-2009 to 01-2011.

Ethical aspects: This pilot study was conducted only after the approval of Institutional Review Board/ Independent Ethical committee agreed by the Indian Council of Medical research (ICMR) respecting GCP (Good Clinical Practice) and following the principles laid down in the declaration of Helsinki and amends thereafter. The investigator institute is authorized to conduct clinical trials and is regularly inspected by the regulatory authorities. Only the subjects who gave informed consent were included in the study.

Inclusion and exclusion criteria: The main inclusion criteria were 1. Participants having all clinical sign and symptoms of acute and recent (less than 72h) sore throat pharyngitis such as exudate and swelling on tonsils or cervical lymph nodes, fever above 100.4°F (38°C), pain and absence of cough with probability of strep pharyngitis above 50% according to the Center criteria [12]. Although, patients were not assigned a specific ICD 10 code, most of the patients were close to the symptoms specified under ICD 10-CM diagnosis code J02.9 and all were positive for Streptococcus culture. 2. Male and female between age groups of 18-65 years, 3. Normal blood biochemical profile for liver and kidney parameters. 4. No history of adverse effect or allergies to any ingredient used in the product composition, 5 Not under any antibacterial or antiviral treatment before recruitment. 6. Given written consent and willing to follow the protocol as recommended.

Randomization: Patients were at randomly assigned by the clinical investigators in each research centre to obtain an approximate ratio of 2:3 for ST and active treatment group at arrival on physical basis.

Study design: Patients in the VB-Th4 group were asked to spray the solution over the throat surface every 20-30 minutes during the 2-3 hours at the beginning of the treatment and 3-4 times per day thereafter up to complete recovery or up to a maximum period of 14 consecutive days. ST group patients followed treatment recommendations advised by their medical advisor.

Efficacy and safety evaluation: After recruitment, the medical history of patient was recorded in the observation file. Upon evaluation of the entire baseline parameters as per study protocol, each patient received the test product and symptom observation diary.

At each time point, all the observations were recorded by an experienced ENT clinical research coordinator or the clinical investigator in collaboration with the patient at each clinical research center.

As the main objective of the study was to measure throat symptom relief efficacy of the test product, the patients treated with VB-Th4 were evaluated for the intensity of throat pain, local throat irritation, and throat redness on a commonly used clinical parameter scoring scale [13] of 0 to 10 where 0 signifies no symptoms, 1-3 mild symptoms, 4-6 moderate symptoms, and 7-10 severe symptoms. Being an osmotically active solution engendering outward flow of liquid and due to continuous deglutition movements of throat, it was not possible to quantify virus amount on the throat surface. Nevertheless, throat swabs were collected to quantify bacterial load by counting the number of colony forming units (cfu/cm$^2$), before 1$^r$ treatment, 2$^r$ after 1$^r$ treatment and then on days 4, 7, 10 and 14 or up to complete recovery. Throat swabs were collected even if the patient was found negative during the previous examination to confirm the results but only positive smears were used to calculate mean values. Results were compared with before treatment values. To verify eventual systemic reactions due to product application, complete hematological and blood biochemical analyses were also performed at the start and at the end of the study.

ST group patients were only checked for the presence of bacterial acute sore throat (throat swab before recruitment), were allowed to
take any treatment prescribed by their clinical ENT specialist and were asked to note any use of systemic antibiotics, duration of antibiotic treatment if any, and the day of complete recovery, if applicable, during the study period. All the participants of both groups were authorized to take systemic antibiotics, if found necessary by the investigator.

Patients from both groups were considered completely recovered when throat surface bacterial count was normal and all the key symptoms of throat infection (pain, irritation, and redness) were absent. Presence of minor coughing was not considered as a key recovery parameter as slight cough always persists even in recovered subjects.

The data obtained from 60 subjects of the VB-Th4 group who completed the study were assessed for the safety and efficacy parameters compared to the results obtained before the start of the study.

**Statistical methods used for data analysis**

Clinical data were analyzed using SAS 9.1.3. Statistical program. The statistical paired sample t-test, Wilcoxon Sign Rank tests were used to compare the laboratory parameter. The Wilcoxon Sign Rank test was used when the normality assumption was false. Descriptive Statistics i.e. Mean Standard Deviation (SD), minimum and maximum frequency distribution were used for the analysis of the demographic details, clinical evaluation, medical history, and laboratory parameters. If the P-value was greater than 0.05, the results were considered to be not significant.

### Results

#### Population analyses

Being a pilot clinical trial, a total 134 patients suffering from acute sore throat were initially screened for the study in four different hospitals in India. As shown in the flow diagram (Figure 4), 17 did not meet inclusion criteria, 6 refused to participate and 2 were unable to come for check up. Among 109 patients enrolled, 63 were at randomly assigned to the VB-Th4 group among which 2 were lost during follow up and 1 did not returned complete data. Among 60 patients who followed complete VB-Th4 protocol, 36 (60.0%) were men and 24 (40.0%) women, between age group of 19-63 years (mean age 46.01 ± 12.84 years), and had a mean body weight of 67.31 kg (± 12.82 kg).

Among 46 other patients included in the ST group, 3 were lost during follow up. Out of 43 results analyzed, 19 (44.18%) were men and 24 (55.81%) were women. All subjects were positive for bacterial cultures at the time of recruitment and the identified organism was mainly Streptococcus. The 43 ST group subjects were taking either one or more treatments such as the analgesics and antipyretics (69.7%), topical antiseptics (48.8%), anti-inflammatory drugs (32.6%), Ayurvedic plant drugs (20.93%) or gargling with warm salted water (16.2%). This group served only to determine the duration of complete recovery and the use of antibiotics.

#### Presence or absence of Strep throat

On day-1 before treatment as well as 60 min after the 1st application

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>Day 1</th>
<th>30-min after 1st application</th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of bacteria</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>20 (p=0.0098)</td>
<td>17 (p=0.0008)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Mean Bacterial count (cfu/cm² ± SD) &gt;1950 ± 179.43</td>
<td>1187.20 ± 127.28</td>
<td>745.60 ± 38.54</td>
<td>374.90 ± 15.50</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

N= Normal values
n= 60 patients

**Table 1:** Number of patients showing positive cultures for strep throat and mean bacterial count (cfu/cm² ± SD) in VB-Th4 group.

**Figure 1:** Number of patients evaluating the intensity of throat pain on a 0 to 10 scoring scale when 0 signifies no pain, 1-3 mild pain, 4-6 moderate pain 7-10 severe pain before treatment, 2h after first product application and on the days 4, 7, 10 and 14 in the VB-Th4 group (n=60).
of VB-Th4, all the patients were positive for the presence of bacterial throat infection, the predominant agent was Streptococcus pyogenes in all the cases. Only 20/60 patients on the day 4 and 17/60 on the day 7 showed presence of bacteria above normal limits. All patients had a normal bacterial count from the day 10 onwards. (Table 1)

Number of bacteria on the throat surface

The number of bacteria measured before VB-Th4 application in throat swabs was very high and above the counting limits of 1950 (±179.43) cfu/cm². 2h after after 1st product application, the mean bacterial count was reduced to 1887.2 (±127.28) cfu/cm² showing a very rapid onset in bacterial reduction. The values were 745.6 (± 39.84) cfu/cm² on the day 4 and 374 (± 39.84 ) cfu/cm² on day 7 with normal values (50-100 cfu/cm²) from the day 10 onwards.(Table 1) This instant and marked reduction in bacterial presence on the throat surface may have been related to the hypertonic osmotically active properties of the basic solution attracting hypotonic liquid from the inner surface of the throat mucosa thereby detaching the microorganisms present on the throat surface.

Effect on pharyngitis symptoms

Almost all the participant in both groups had moderate to severe throat pain, throat irritation and inflammation at the start of treatment. These parameters were evaluated only in the VB-Th4 group.

Effect on throat pain

57/60 patients had moderate to severe throat inflammation at the start of the study (Figure 1). A marked analgesic effect was observed, within 2h after the 1st test product application as only 2 patient recorded severe pain and the pain intensity was reduced to moderate (34/60) or mild (23/60) in other patients. The number of patients with moderate pain was slightly increased on the day 4 (40 instead of 34 noticed 2h after the 1st application) but was constant in the severe pain group. A significant change was seen from the day 7 where 91% patients (55/60) had only mild pain and on the day 10 where most of the patients (58/60) had no throat pain.

These results show a very strong initial analgesic type of effect of the test product followed by progressive reduction between days 1 and 4. As most of the patients (40/60) had nearly no bacterial infection just after the 1st product application, it can be concluded that although VB-Th4 exert a nearly instant anti-bacterial effect, the effects of VB-Th4 on the throat pain reduction are not instant. This may be related to the fact that pain is usually a consequence of topical inflammation which diminishes progressively.

Effect on throat irritation

As shown in the Figure 2, on the day 1 before treatment, 32/60 patients had severe and 24/60 patients had moderate symptoms of throat irritation. This sensation was reduced in most of the patients just after the 1st application of the product but was not completely disappeared. A progressive reduction in the throat irritation score was observed up to the day 7 when almost all the patients (55/60) were completely recovered.

Effect on throat redness/inflammation

The throat inflammation was progressively diminished during the first 4 days of treatment and only 6/60 patients had severe to moderate inflammation from the day 7 onwards. (Figure 3) The results of this parameter correspond to the concomitant reduction of pain and bacterial infection observed in the same patients.

Complete recovery period compared to the ST group

As shown in the Table 2, the number of patients who stopped all treatments after 2 days as they felt completely recovered was 31% in the VB-Th4 group (n=60) compared to only 11% in the ST group (n=43). On the day 7 of treatment, 61% participants in the VB-Th-4 group stopped treatment compared to 25% in the ST group. On the day 10 almost all the patients (95.0%) in the VB-Th4 group stopped treatment (57/60) compared to 28/43 patients (65.1%) in the ST group. Only 1 patient was not completely recovered in the VB-Th4 group on the day 14 and still had moderate to severe symptoms of throat pain, irritation, and inflammation without the presence of bacterial infection. This patient was diagnosed for pneumonia and was kept on antibiotherapy thereafter. 9/43 patients in the ST group were not completely recovered.

[Graph showing the number of patients scoring the intensity of throat irritation on a 0 to 10 scoring scale (0 = no irritation, 1-3 = mild irritation, 4-6 = moderate irritation, 7-10 = severe irritation) just before treatment, 2h after first product application and on the days 4, 7, 10 and 14 in the VB-Th4 group (n=60).]
on the day 14 indicating that the recovery is much faster in the VB-Th4 group especially when the treatment was started during the early phase of throat infection. These results correspond to the absence of bacterial infection observed in most of the patients right after the 2nd day of treatment.

**Antibiotherapy in the VB-Th4 compared to the ST group during the study**

As indicated in the Table 3, the number of patients requiring antibiotic therapy was much higher in the ST group compared to the VB-Th4 group. During the 14-day study period, only 4/60 patients...
(6.66%) in the VB-Th4 group required antibiotic therapy for an average duration of 7.1 day compared to 14/43 patients (32.56%) in the ST group for an average period of 9.8 days. On the day 14, only 1/60 patients in the VB-Th4 group was still continuing antibiotic therapy compared to 7/43 (16.23%) in the ST group. These results show that the probable rate of serious complications requiring antibiotic therapy is markedly reduced in the VB-Th4 group with respect to the number of patients and the duration of treatment.

**Other observations**

No side effects or any undesirable reaction was observed in any of the patients. None of the haematological, blood biochemical, or renal parameters was affected in the VB-Th4 group. Most of the patients felt an increase of liquid secretion in the mouth and throat by the end of day 2 onwards.

**Discussion**

Viral and bacterial throat infections are usually seasonal epidemics all over the world affecting 5-15% of the population [14]. This imposes a considerable economic burden in the form of hospital and other health care costs and lost productivity. In most of the cases, initial viral infection, particularly the influenza virus, is the main cause. After initial virus contact with the upper respiratory tract mucus membrane, virus multiplies in a few cells and cell lyses liberates a large amount of free virus particles on the throat surface. These newly liberated virus particles attach new healthy cells, multiplies, and weakens local immunity followed by secondary bacterial infection. Viral throat infection usually leads to sore throat which is characterized by throat pain, discomfort, or throat irritation, running nose, and cough. These symptoms may be followed or associated with Streptococcal pharyngitis or Streptococcal sore throat, caused by group A Streptococcus bacteria resulting in fever, patches of pus on the throat surface, and swollen lymph nodes [1]. Patients opt for treatment only during later stage when bacterial infection and clinical signs of pharyngitis are well established. Symptoms may last for 2-3 weeks in untreated patients.

In the absence of any effective topical antiviral drug, intracellular antivirals can be used but they take at least 3-4 days to exert their effect and are of no use except to reduce the duration of symptoms by one or two days [15]. Although these drugs are very effective to prevent the viral infection, they are expensive, have many side effects, and patients are usually reluctant to take any preventive medication. Antiviral vaccines are useful but due to frequent minor genetic changes, known as antigenic drift, vaccines require annual reformulation and can be used only in the developed countries [16,17]. Therefore treatments such as topical antiseptics, expectorants, local anesthetics, mucolytic drugs, or salt water gargles are commonly used to relieve symptoms. Antibiotic therapy is employed in nearly 50% sore throat patients for an average duration of 10 days to prevent or to cure secondary Streptococcus infection [18] but all these treatments have no effect on millions of free virus particles present on the throat surface and responsible for initiating and maintaining the infection.

Therefore, the scientific approach to treat viral throat infection lies in neutralizing the virus particles on the throat surface, in inhibiting viral entry into the host cells, and in removing bacterial infection simultaneously.

Unfortunately, due to the complexity of the influenza virus envelop with at least 16 haemagglutinin and 9 neuraminidase Gps, due to simultaneous involvement of different proteases in the viral entry [4] and subsequent secondary bacterial infection, it is practically impossible to find a single drug with can act on all these parameters at a time.

As the virus surface Gps and proteases are protein in nature and as certain specific plant PCDs have a strong affinity to bind with the proteins, the aim of our research was to employ the PCDs as topical non specific antiviral agents. Virus Gps and virus entry enhancing enzymes were identified by incubating more than 350 individual PCDs with virus or with proteases and analyzing their effect on virus growth in vitro. Only 8 among 350 PCDs were found active and only 2/8 PCDs isolated from Vitis vinifera seeds and Sambucus nigra fruits were capable to inhibit virus growth above 90% in vero cells. These PCDs (0.78%) were incorporated in a hypertonic, viscous solution so as to generate an osmotically active film over the throat surface attracting hypotonic liquid from the throat mucosal surface and detaching the bacteria due to this mechanical effect. Honey was added to improve the viscosity and anti microbial activity of VB-Th4. Such a product could

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° VB-Th4 % population</td>
<td>60</td>
<td>0</td>
<td>19</td>
<td>31.86</td>
<td>61.66</td>
<td>57</td>
</tr>
<tr>
<td>N° standard treatment (ST) group % population</td>
<td>43</td>
<td>0</td>
<td>5</td>
<td>11.62</td>
<td>25.58</td>
<td>65.11</td>
</tr>
</tbody>
</table>

a: The patients not recovered completely after the day 14 were not followed. The difference is statistically significant compared to the ST group (p<0.05) from the day 2 onwards.

<table>
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<tr>
<th>Group</th>
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<th>Day 7</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° VB-Th4 % population</td>
<td>60</td>
<td>0</td>
<td>2</td>
<td>3.33</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N° standard treatment (ST) group % population</td>
<td>43</td>
<td>2</td>
<td>13</td>
<td>4.65%</td>
<td>30.23</td>
<td>32.56</td>
</tr>
</tbody>
</table>

a: The patients not recovered completely after the day 14 were not followed. The difference is statistically significant compared to the ST group (p<0.05) from the day 1 onwards.
have topical virus neutralizing, protease inhibitor and antibacterial activities simultaneously.

The results of this study clearly show that VB-Th4 exert nearly instant effects to reduce the number of bacteria on the throat surface. The rapidity of anti-bacterial effect indicates a physical effect of outward exudation of hypotonic liquid, creating a flux of liquid towards the outer part of the throat surface and subsequent bacterial detachment. Patients comments concerning heat sensation on the throat surface and excessive liquid flow from the throat during the first 5-10 minutes after each product application also confirms this mode of action.

Although the amount of virus particles on the throat surface was difficult to measure, it is very likely that the free virus particles were also cleaned from the throat surface reducing or stopping new throat cell infection. The marked reduction observed in the symptomatic parameters of throat infection such as pain, reddish color indicating inflamed mucosa, and throat irritation also indicate absence of new virus infection which may have been related to PCD binding with the virus Gps and proteases. Experiments conducted during the research phase indicated that the selected PCDs neutralize above 80% of influenza virus particles and the proteases when PCDs were pre-incubated for 30-minutes with virus suspension or selected proteases before vero cell infection in vitro [8]. Reduction in throat bacterial count and new viral infection helps rapid recovery thereby reducing the requirement of antibiotic therapy by nearly 50% compared to the ST group.

No side effects or local reaction was noticed in any of the patients, suggesting that VB-Th4 solution is a safe and nearly instant therapy for the virus originated throat infections. Due to the mechanical mode of action of this product, VB-Th4 can be considered a non specific treatment for the throat infections of viral or bacterial origin. In the absence of any topical, safe, inexpensive and effective topical antiviral drug, the use of topical viral Gp inhibitors in association with protease inactivators may constitute a new promising therapeutic approach for viral and bacterial throat infections.

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