Clinical Efficacy of Novel Filmogen, Antimicrobial, Cleaning, Fluidizing Cough Treatment

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Abstract

Objective: Cough reflex is the body’s protective mechanism to prevent entry of foreign material into the lower respiratory tract. Cough is usually caused by a primary viral infection: virus growth causes lysis of throat mucosa cells, leading to inflammation, secondary bacterial infection, accumulation of contaminants on the throat, increased mucus secretion, and coughing. To treat this multifactorial condition, an effective treatment should be multitarget, but no currently available drug fulfills this complex yet essential requirement. We developed a hypertonic, highly osmotic, filmogen liquid bandage which can mechanically clean the throat surface. A clinical trial was conducted to evaluate its efficacy and safety.

Methods: A 14-day, randomized, placebo-controlled, double blind, efficacy and safety study was conducted on 37 treated vs. 17 comparator (saline solution) patients suffering from dry cough. Products were applied as spray, 3-4 times daily, for maximum 14 days, and cough-related parameters were evaluated on days 1, 2, 3, 6, 9, 12, and 14.

Results: Compared to the comparator product, test product triggered an instant and strong reduction in the mean scores of dry cough severity and frequency, and consequently in throat pain, irritation, swelling, and redness, with remarkable improvement in Leicester cough questionnaire parameters. Test product proved as safe as the comparator product.

Conclusions: Cleaning the throat surface and fluidizing mucus using a new generation of liquid throat bandages opens new therapeutic horizons for the treatment of severe cough.

Keywords: Clinical trial; Filmogen glycerol; Dry cough; Wet cough; Liquid bandage

Introduction

Coughing is the upper respiratory tract (URT) defence mechanism to stop undesired materials from entering the lower respiratory tract (LRT). In the vast majority of cases, an initial viral infection (rhinovirus, influenza) causes URT mucosa damage which is followed by secondary bacterial invasion [1,2], release of pyrogenic endotoxins and super antigens, activation of T lymphocytes, and liberation of multiple interleukins and pro-inflammatory cytokines such as tumor necrosis factor and gamma interferon [3,4], leading to the accumulation of waste products over the throat mucosa, and consequently throat inflammation, irritation and coughing. Being a multi-factorial disease involving various aetiologies and progressive pathogenesis, it is not easy to establish the triggering cause of cough. As a defense mechanism, the URT produces mucus which is normally sticky and helps to keep the air passage humidified so as to minimize irritation, but also traps bacteria, and contains defensins, lysozymes and natural antibiotics to fight infection [5]. Cough can be acute if onset is sudden and if it is present less than 3 weeks, sub-acute when it is present between 3 and 8 weeks, and chronic when lasting longer than 8 weeks. It can be productive or wet when sputum is coughed up, or non-productive (dry) with very sticky mucus. High infection initially leads to overproduction of mucus, but if the infection becomes chronic, the airway epithelium becomes covered by bacterial and cellular waste products, leading to the development of dry cough [6]. Dry cough can also be caused by diseases like asthma, medications like ACE inhibitors, or gastro oesophageal reflux disease (GERD) where stomach acid is passed onto the throat causing the throat surface to become dry and irritated, while wet cough is commonly due to upper respiratory tract infections [7]. Therefore, an ideal treatment for dry cough should clean the URT mucosa and fluidize sticky mucus so as to minimize throat irritation and the cough reflex, and allow natural healing processes to repair the damaged mucosa and improve local defences.

Unfortunately, none of the currently available treatments is directed at fulfilling these basic requirements. Commonly used treatments include antitussives that help block the cough reflex, expectorants that increase the amount of phlegm produced by the lungs, to make secretions easier to expel by coughing, antihistamines to reduce inflammation, or decongestants that constrict URT blood vessels so as to reduce congestion [8]. These drugs have multiple side effects, they act only symptomatically, and many scientific studies show that they have little benefits regarding relief of cough. Other home treatments include analgesics, antibiotics, mucolytics, phytotherapy, application of honey on the throat, but one of the most universal and inexpensive
treatments consists of salt water gargling which is considered to be the safest and relatively efficient symptomatic treatment [9,10]. Salt water acts through its osmotic and cleaning properties on the throat surface, by minimizing the number of contaminants and by hydrating the throat surface. Salt water may also help fluidize sticky mucus to some extent, but its use is fairly limited, as solutions containing up to 3.4% NaCl have poor osmotic activity whereas higher concentrations are highly irritating to the URT mucosa, generating an excessive secretion of histamine and methacholine [11]. Secondly, salt water’s duration of action is too short and requires frequent gargling, which proves impractical. Therefore, the aim of our research was to find a safe, non-irritating, highly osmotic solution which could be applied on the URT mucosa. We conceived a new glycerol-based solution (VB-Gy), nearly 18 times more osmotically active than sea water yet not too irritant [12]. To further improve the duration of action of VB-Gy, a very small quantity of a specific VB-Gy-binding polymeric association, as well as some hydrophobic essential oils, were introduced into VB-Gy to improve its filmogenicity, flexibility and resistance to out-flowing hypertonic liquid. This filmogen solution was patented and termed as F-VB-Gy [13].

F-VB-Gy is a natural antiseptic and cell-friendly solution, an ideal therapeutic candidate, capable of exerting sufficient osmotic pressure over the semi-permeable throat mucosa without being irritating or cytotoxic. Topical application of such a solution should attract hypertonic liquid from the inner part of the throat, thereby detaching contaminants and fluidizing sticky mucus, so as to reduce throat irritation, stop the cough reflex, and prepare a favorable ground for natural healing of damaged URT mucosa.

Representing a new generation of mechanically acting, hypertonic, osmotically active, filmogen solutions, F-VB-Gy’s clinical efficacy and safety were assessed in patients suffering from chronic dry cough.

Materials and Methods

The clinical part of this research was conducted at Nexus Clinical Research Center in India, affiliated to Nexus Clinical Research LLC, USA. The protocol and the study design were approved by the Institutional Ethical committee of India-Rajiv Gandhi Institute of medical sciences (EC Registration No. ECR/492/Inst/2013 of 05-12-2013) and the trial was performed following the ICH-GCP guidelines as per the declaration of Helsinki to conduct ethical research on human subjects.

Study design and rationales

The study was designed as a multi-centric, randomized, placebo-controlled, double blind, clinical trial. The aim of the study was to compare the efficacy and safety of F-VB-Gy osmotic filmogen spray (TP) to saline solution as comparator product (CP), in patients suffering from severe cough. The TP was first assessed for risk evaluation and conformity to essential requirements as per EU Directive 93/43/EEC. The aim was to obtain final results on at least 18 patients in the CP and 36 in the TP group so as to have sufficient data for statistical analyses of results. The doses were selected based on a previous pilot dose range finding observational study in patients suffering from sore throat infection with cough, where TP or CP were applied as 3-4 sprays over the throat surface, every 30 min in the beginning of the treatment during the first 2 h, and 3-4 times per day afterwards. Being commonly used home treatment; saline solution was selected as CP. Products were applied for a maximum period of 14 days or up to complete healing.

Inclusion and exclusion criteria

At the time of recruitment in different study centers, patients were examined physically and patient’s medical, surgical, and allergic history was checked. Vital signs such as blood pressure, pulse rate, and respiratory rate were recorded. Patients not suffering from any serious pathology were then examined for study inclusion and exclusion criteria. The main inclusion criteria were: presenting all clinical signs and symptoms of severe dry cough, sore throat with pain, and inflammation; male and female in the 18-65 years age group; normal blood biochemical profile for liver and kidney parameters; no history of adverse effect or allergies to any ingredient used in the product composition; not under any antibacterial or antiviral treatment before recruitment; and ready to give written consent for study participation and willing to follow the protocol as recommended.

The main exclusion criteria included: presence of any respiratory disease; being under medication; having a known allergy to test product (TP) components; and lack of willingness to participate in the study.

Randomization

After screening, patients satisfying all the inclusion criteria were enrolled and randomly allocated in 2:1 ratio as per randomization schedule to receive TP or CP (0.9% NaCl solution as comparator product). Treatments were allocated to patients by carrying out randomization using SAS Version 9.1.3 following a randomization schedule. Block Randomization methodology was employed for generating the list.

Product presentation and administration

TP and CPs were supplied by Vitrobio, France (Issoire) and were presented identically (30 ml aluminum spray containing slightly viscous and colorless liquid) except for the product code and the batch number. The TP contained an aqueous F-VB-Gy solution containing a specific association of dry cough CD-cyanidins, while CP contained 0.9% NaCl.

Parameters studied

The primary outcome was defined as effects on dry cough severity and cough frequency, as well as changes in throat irritation, throat pain, effect on throat swelling, throat redness and related parameters, which are summarized in Leicester Cough Questionnaire (LCQ) for cough-related quality of life. Changes were evaluated on a rating scale of 0 to 10 (0 indicating absence of symptoms) just before 1st treatment, after 5 min and 2 h, and on day 1, 2, 3, 6, 9 and 14 by the investigator (day 0, 1, and 14) or by the patients. Screening values were considered as baseline values and for ethical reasons, treatment was started just after patient’s enrolment in the study (day 1). Each patient received a unique screening identification number, randomization code, and enrollment identification number.

Safety assessment: At the end of the study, subjects and investigators evaluated the adverse effects, tolerability and acceptability of TP and CP.
Statistical analysis of results

The analyses were conducted with Microsoft Excel and XLStat using the available data. Significant effects were those with a probability lower than α=0.05. For each score, repeated measures analysis of variance (RMANOVA) determined differences in symptoms scores across study visits. Nemenyi post-hoc test provided pairwise comparisons in a group between baseline and the end of the study.

Demographics

Demographic distribution flow chart shows that the population enrolled was corresponding to the study protocol (Figure 1).

![Figure 1: Demographic distribution flow chart.](image)

Among 59 patients enrolled in the study, 17 in the CP group and 37 in the TP group completed the study. No patient was withdrawn due to any undesired effects but 2 patients in CP and 3 in TP were lost to follow up during the study. The male to female ratio was 10:7 in CP and 19:18 in TP. The demography of patients included in the study was considered comparable between the two groups.

At the time of recruitment, all subjects were diagnosed for moderate to severe dry cough, were positive for throat swab bacterial cultures with Streptococcus as main causative organism. Only those patients having dry cough since less than 72 h, of any origin with related symptoms as throat pain, throat redness, throat irritation/itching, (fever if present), were included in the study to obtain a homogenous population. Patients with diagnosis of diseases of the lower respiratory tract: inflammation of the larynx, trachea, bronchi, pneumonia, asthma, sinusitis, allergic rhinitis, as well as heart disease was not enrolled in the study. Participants were asked to refrain from smoking during the treatment period but this parameter was difficult to quantify. The baseline mean symptom scores in the TP and CP groups were nearly identical in both groups but the severity of dry cough was slightly (<10%) higher and throat pain intensity was slightly lower in TP compared to CP as shown in the figures.

Results

Requirement for antibiotics and antimicrobial effects

When no improvements were observed, coughing persisted with whitish deposits on the infected throat surface; investigators were allowed to use antimicrobial medications.

Antibiotics were prescribed, at the investigator’s discretion, when lack of improvement or aggravation in the dry cough-related symptoms was noted and bacterial cultures were positive. Results show that the requirements for antibiotics was strongly diminished in the TP group (10.81% patients) compared to the CP group (82.35%).

The start of antibiotherapy was between days 9-11 for 3 patients in each group while 11/14 patients in the CP and 1 out of 4 in the TP group, were given antibiotics from day 11 onwards. The duration of antibiotic treatment was fairly comparable in both groups (Table 1).

| Antibiotherapy | CP Control group (n=17) | TP Treated group (n=37) |
|----------------|-------------------------|-------------------------|
| Number of patients | 14/17 | 4/37 |
| % | 82.35% | 10.81% |
| Mean duration (within the study) | 2.64 days | 2.25 days |

Table 1: Summary of antibiotherapy needs.

Effects on dry cough severity

In the saline spray-treated CP group (n=17), there was nearly no change in the mean score up to day 6 (-6.20%). The cough severity was then slightly reduced from day 9 (-11.51%) up to day 14 (-22.13%) but the results are not statistically significant (NS). This slight and progressive reduction in the mean values is more probably related to the natural healing process and to the use of antibiotics in some patients. These results show that treating dry cough with saline solution has nearly no significant beneficial effect on cough severity (Figure 2).

![Figure 2: Mean scores (± SEM) for cough severity in Test Product group (light gray) vs. Comparator Product group (dark gray) just before treatment (baseline T0) and on Days 1 (5 min & 2 h after 1st application), 2, 3, 6, 9, 12 and 14. *p<0.05, **p<0.01, ***p<0.001 for TP compared to CP at the same time point, and <0.05 compared to baseline values.](image)

In the TP group (n=37), there were no beneficial effects on dry cough during the first 2 h but a drastic reduction was observed from day 2 (-15.81%, NS) with further improvement on day 3 (-32.08%), day
In the TP group, the cough frequency was not changed on day 1 (-2.13%) but a strong and continuous reduction was observed from day 2 up to the end of the study (p<0.001). In this group, nearly 50% reduction in the cough frequency was observed right on day 6 and almost all the patients (98%) had recovered on day 14. Although this reduction in cough frequency is excellent, it should be noted that the TP does not totally suppress the cough reflex within the first week of treatment but requires about 12 days for dry cough to disappear in 80% of the patients treated.

**Throat irritation**

In the CP group, the throat irritation score hardly evolved during the 1st 12 days of treatment (-13.0%) as the mean reduction was -5.4, -7.6, -10.9, and -13.1%, on days 3, 6, 9, and 12 respectively (NS). As many patients (14/17) in this group started taking antibiotics during the last week of the study, moderate decrease (-32.6%, p<0.05) in mean score observed on day 14 is considered very likely to be due to the antibacterial effects of antibiotics.

In the TP group, a marked (-7.5%) reduction in throat irritation was observed only 2h after the first product application, which in all probability is due to the cleaning and hydrating properties of the TP. This is further confirmed as from day 1 onwards, the mean score of throat irritation/itching showed constant and significantly strong decrease up to the end of the study (Figure 4). The mean reduction on days 3, 6, 9, & 12 was nearly 40, 60, 80, & 90% (p<0.01 from day 2 onwards) compared to the starting score, (with mean scores lower by 37.8%, 55.4%, 73.4%, & 89.7% than those of CP group during the same time period) indicating a strong effect of the TP on throat irritation. All patients had recovered on day 14. These results correspond to the concomitant improvements observed in other dry cough symptoms with the TP treatment.

**Dry cough frequency**

The results of the cough frequency in the CP group show a pattern (Figure 3) of recovery comparable to the effect on cough severity as the cough frequency in this group was not changed up to day 6 (only 5.79% reduction) and decreased progressively but very slightly during observations made on days 9, 12 and 14 (-11.57, -18.33 and -27.01%, p:NS) respectively. Even after 14 days of treatment, the efficacy of treatment in this group was limited to about 27% (p<0.05), indicating that saline solution and/or antibiotic treatment may help only slightly in reducing cough frequency. Total recovery was not achieved within the study period, leading to the conclusion that such treatment appears not significantly effective or should perhaps be prolonged further (more than 14 days).

**Throat pain**

In both groups, pain intensity was not significantly affected during the 1st day of treatment.

Subsequently, in the CP group, mean pain intensity decreased progressively and very slowly through the study period. In this group, reduction in pain intensity compared to baseline was 13.4% on day 6, 15.7% on day 9, 21.3% on day 12 and 33.6 % on day 14 (p<0.05 on day 14). These findings (Figure 5) show that spraying saline solution on the dry throat surface does not significantly speed up the natural course of the condition. Although administering antibiotics does seem to help, as symptomatic manifestation of dry cough-induced throat pain is eventually reduced by about 32%, the saline solution appears to be moderately efficient but not sufficiently to alleviate throat pain significantly, even after 14 days of treatment.

In the TP group, a strong reduction in the mean pain intensity was observed between days 2 and 3 (-19% and -38% compared to pre-treatment, continuing regularly thereafter (-56% on day 6, -72% on day 9, and -86% on day 12), to nearly completely disappear on day 14 (-99%). This evolution was strongly significant, as the pain intensity was lower in TP group by about 50% on day 6, 80% on day 12, and 98% on day 14, compared to CP group. The difference is statistically significant from day 2 (p<0.01) up to day 14 (p<0.001).

These findings correlate with the results of other parameters measured in this study, indicating that the TP may constitute a good topical product to treat dry cough and its related symptoms such as throat pain.
In the CP group, except for some notable reduction (-7.9%) on day 2 compared to T0 mean values, there was no significant reduction between days 3 and 9. Throat swelling was noted slightly low between days 12 to 14 (p<0.05), as shown in Figure 6.

In the TP group where only 4/37 patients took antibiotics from day 1 to day 6. In the TP group, there was no change in this parameter on day 1 but subjects noticed a highly significant (p<0.05) reduction of nearly 19% on day 2 (NS), 60% on day 6, 77% on day 12 and almost 98% on day 14 compared to T0 mean score. This difference is also statistically significant compared to CP at all-time points, but between 6 and 9 days of treatment are required for complete recovery of patients.

The mean score of throat redness followed the same pattern of swallowing difficulty as very slight but progressive reduction was observed in CP group only from day 3 (-3.8% on day 3 and -14.2% on day 6) up to day 14 (-37%, p<0.05) compared to T0 values. In the TP group, throat redness was only slightly decreased on day 1 (-5.5%) but a significant (p<0.05 from day 3 onwards) and progressive reduction was observed from day 2 (-27%): -48% on day 3, -70% on day 6, around -90% from days 9-12, and nearly total disappearance on day 14. Compared to the CP group values, throat redness in the TP group was lower by 26% as early as on day 2; 46% on day 3; 66% on day 6; and 86% on day 9, indicating strong efficacy of the TP on this symptom.

Patient quality of life assessment

On screening visit, patients received Leisters Cough Questionnaire for scoring their Quality Of Life (QOL) related to cough. The QOL score was drastically improved in the TP compared to CP group indicating that TP was very effective in treating dry cough, which resulted in significantly improved Quality of Life of patients. No side effects were noticed in any of the patients in both groups.

Adverse effects, tolerability and acceptability

No adverse effects were notices in any of the patients, neither in TP or CP group, during the study period. Just after each product application, a few patients observed a slight sensation of warmth on the throat surface only in the TP group for about 1-2 min. This strong effect on throat swolleness is most probably related to the hypertonic properties of the TP solution.
significant difference in vital signs, laboratory test values or general/systemic examination results during study period compared to the baseline data.

Complete recovery at the end of the study

As shown in the Table 2, the symptoms of dry cough were drastically diminished in the TP compared to the CP group indicating that the TP is not a general symptom specific treatment but it improves overall symptoms of dry cough.

| Group   | Severity | Frequency | Irritation | Pain | Swollen throat | Easy swallowing | Throat redness |
|---------|----------|-----------|------------|------|----------------|-----------------|---------------|
| CP%     | 17.65    | 23.53     | 23.50      | 23.53| 23.53          | 29.41           | 23.53         |
| TP%     | 75.68    | 89.19     | 97.30      | 94.59| 97.30          | 89.19           | 100.0         |

Table 2: % of population in the CP (n=17) and TP (n=37) groups showing total recovery for individual dry cough symptom at the end of the study. Results are expressed as % mean difference in each group compared to the baseline values of the same group. Note: These symptoms were noted as moderate to severe by all the patients at the time of recruitment.

Discussion

Chronic or dry cough is not a life-threatening disease in most of the cases but it affects seriously the healthcare budget and the quality of life [14-16]. This is a topical and multi-factorial pathology, requiring a pluri-targeted treatment approach [17]. An ideal treatment should not only stop viral infection but should simultaneously act as antiseptic, antibacterial, cleaning, hydrating, mucus fluidizing, epithelial cell-regenerating, cough reflex-suppressing, non-irritant and totally safe treatment. Any drug having only one or two of these properties will provide only symptomatic relief but will not eradicate the disease rapidly. As it is practically impossible to incorporate all these essential cough treatment requirements in a single molecule or drug, currently there are only symptomatic treatments available [18].

It should also be considered that dry cough is not a systemic but a topical pathology as viral growth and cellular destruction occur in throat mucosa cells, bacteria attach on the mucosa, inflammatory and pro-inflammatory cytokines are liberated on the surface, and the resulting waste products pass from the URT into the LRT [19,20]. In such cases, treatment should be more effective and less toxic if it is applied directly on the URT. Apart from a few antiseptics, antibiotics, and phytotherapy drugs, saline gargling or honey application, all other supposedly effective treatments are administrated orally [21]. Most of these systemic drugs have central-acting cough reflex-suppressing properties but they eventually produce a multitude of side effects such as dizziness and nausea, without any effect on multifactorial cough parameters, which is however essential for an efficient treatment [22,23]. This is the reason why natural remedies are preferred as they have a better benefit/risk ratio [9]. Salt water gargling is still commonly used and is considered one of the best and safest treatments for cough [24]. Salt water gargling, containing up to 3.4% NaCl, is found to be even more effective than antibiotics or analgesics for dental infections [25], sore throat, and wound healing, compared to chlorhexidine [26]. The results of this study show that in the CP group, although spraying saline solution on the throat is relatively effective in providing symptomatic relief, the improvements are only short-lasting and incomplete. Better results were only obtained when CP was associated with systemic antibiotics. Salt water acts through its osmotic, hydrating and fluidizing properties as osmosis attracts hypotonic liquid from the inner parts of the throat and this liquid flow helps humidifying the throat and reducing contaminants over its surface, thereby minimizing irritation and the cough reflex. Being poorly osmotic, salt solutions require 4-6 gargling sessions per day for at least 10-15 days to get progressive improvement, which is not very practical and explains why salt water gargling is not so commonly used. It's also not possible to increase the salt concentration above 3.4% NaCl to ameliorate the hypertonicity of gargling solution as this would render the solution highly irritant and cause throat inflammation [11]. This is the reason why we concentrated our efforts on finding a new generation of topical treatment which acts like salt solution but which is non-irritant and much more osmotic compared to 3.4% salt solutions to create a strong flow of hypotonic liquid from the throat tissue, and is of detaching and draining instantly all the contaminants present on the URT. Being a mechanically acting solution, such a product will not enter the cells nor the circulation, and will not have side effects. During our initial research, we formulated VB-Gy, a glycercol-based, colorless, viscous solution, which is 18 times more osmotically active than sea water yet non-irritant to the throat mucosa. The non-toxicity of glycercol is proven as it is used to preserve canned food, to deep-freeze live cells and tissues, and as an antibacterial agent [27]. Even if VB-Gy is diluted to 50%, it still remains 9 times more osmotic compared to sea water, which is highly sufficient to attract hypotonic liquid from a live biological surface and to detach contaminants. Although VB-Gy has higher filmogen properties than sea water, it too gets easily diluted (within a 5-10 min) due to its higher osmotic properties, and the remaining activity is not strong enough to keep the URT clean over a longer period of time. This inconvenience was resolved by selecting a few natural or synthetic polymers having an affinity for VB-GY molecules. The polymers (≤1.0%) were added to VB-Gy solution to make it more filmogen and flexible (F-VB-Gy) as described by Shrivastava et al. [13]. The filmogenicity and resistance of F-VB-Gy can further be improved by adding small quantities of hydrophobic essential oils or highly branched cellulosic polymers. As dry and wet coughs require different treatment approaches, the specific polymeric associations prepared for these treatments were termed CD-cyanidins for the treatment of dry cough or CW-cyanidins for the treatment of wet cough.

Results of this clinical study clearly show that F-VB-Gy, CD-cyanidins–containing, filmogen spray is much more active compared to saline solution in reducing dry cough frequency, severity, throat irritation, pain, swelling, and redness, with nearly 50% reduction in all symptoms within 3-6 days and 80-85% in less than 2 weeks. This
treatment also dramatically reduces the need for antibiotic therapy as only 11% patients in TP group needed to be prescribed antibiotic therapy compared to 82% in the CP group. As antibiotics are generally prescribed when investigators observe whitish deposits on the throat surface indicative of microbial growth, minimized requirement of antibiotics in the TP group shows powerful antimicrobial properties of TP. It is postulated that cleaning the throat surface of microbial and other contaminants accelerated natural healing process and the frequency and severity of dry cough symptoms. The LCQ demonstrates a significant improvement in the quality of life of the patients, and the total safety of the TP. Such a therapy is particularly useful to avoid using centrally-acting antitussive drugs such as codeine, morphine or antihistamines, peripherally-acting bronchodilators or anesthetics, systemic antivirals such as amantadine or acyclovir, anti-inflammatory or antibiotics [11]. One should not forget that the URT mucosa is highly damaged with abundant bacteria and dead cells on its surface, leading to poor local defences and the development of chronic, persistent cough. Almost all systemic drugs induce side effects and cause more harm than good, whereas topically applying any chemical treatment of other topical diseases for which there is still no effective treatment available.

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Conflict of Interests

The authors have declared that no conflict of interest exists.

Declaration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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