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Original Research Article

Efficacy and tolerability of Arnophyte cream for herpes infection, in subjects with early signs and symptoms of recurrent HSV-2

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ABSTRACT

Background: Arnophyte® cream developed from *Ficus arnottiana* plant extract showed strong potential as an Anti-viral agent. The objective of the study was to evaluate the efficacy and tolerability of Arnophyte® cream in subjects with early signs and symptoms of recurrent HSV-2.
Methods: The treatment was given for a period of 14 days. The study outcomes measured were assessment of reduction in pain using the visual analogue score (VAS), the changes in the quality of life index for recurrent genital herpes (GHQoLr); physician's and patient's global assessment of the therapy, signs and symptoms associated with HSV-2 and healing of the target lesion on baseline, day 2, day 4, day 7 and day 15.
Results: Arnophyte® cream showed significant reduction in the signs and symptoms of herpes infection. The cream was well tolerated with no serious adverse events observed.
Conclusions: Arnophyte® cream can be considered as a possible therapeutic option for the treatment of recurrent herpes infections in both HSV-1 and HSV-2.

Keywords: Herpes, HSV, Clinical study, Anti-viral, Arnophyte cream, *Ficus arnottiana*

INTRODUCTION

Viral infections, with particular reference to herpes infections, pose a major threat to mankind. Herpes simplex viruses (HSV) are evolutionarily ancient and ubiquitous. HSV-1 is commonly associated with oral herpes known as cold sores or fever blisters.[1] The oropharynx is the most common site of infection caused by HSV-1. HSV-2 is usually spread sexually and occurs in the anus, rectum, upper alimentary canal as well as the genital area with seeding of the sacral ganglia. HSV-2 viral replication starts locally in the genital epithelium and thereafter ascends to the sensory nerves and to the sacral ganglia, where latency is established. Systemic symptoms, including headache, fever, myalgia and backache occur in about 70% of women and 40% of men seeking medical care for primary genital herpes. These symptoms peak during the first 4 days of infection and abate over the subsequent 7 to 10 days. Itching and local pain often precede visible lesions by 1 to 2 days. Lesions erupt over 7 to 8 days and evolve from vesicles and pustules to wet ulcers over approximately 10 days; crusting and healing follows over the ensuing 10 days. However, when symptoms do occur, they tend to be more severe with primary compared with recurrent infections.[2-4]

Genital herpes disease is of public health importance due to its morbidity, frequency of recurrence and the rare but serious neonatal disease that may occur following intrapartum transmission of HSV.[5] The prevalence of herpes infection has increased, despite fairly widespread use of antiviral drugs.[6] Worldwide rates of HSV infection - counting both (HSV-1) and (HSV-2) - are between 65% and 90%.[7] It is estimated that approximately 22% of American adults and as many as 30% of adults worldwide are seropositive for HSV-2.[8,9] An estimated 536 million people aged 15-49 are infected with the herpes simplex virus type 2 (HSV-2) worldwide.[10] Higher seroprevalances have been reported in many parts of the developing world.[11] In India, genital herpes has emerged as one of the most predominant STDs, and is the leading cause of genital ulcer diseases (GUDs).[12-14] There has been a general increase in the transmission of viral diseases (STIs), especially HSV-2 and HSV associated GUDs as reported by studies.[15,16] Although reports vary across different regions, a survey has shown that in India 33.3% of individuals are seropositive for HSV-1 and 16.6% are seropositive for HSV-2. Those with both HSV-1 and HSV-2 antibodies are estimated at 13.3% of the population (total of 63% of the population). Indian men are more likely to be infected with HSV-2 than women, and increasing seroprevalence of this virus is associated with an increasing age.[17]

Control of viral infections remains an unachieved goal, due in part to the limited availability of effective anti-viral drugs and measures. Acyclovir (ACV) is the most used chemotherapy agent against HSV-1 and HSV-2, in systemic or topical therapy. Other clinically relevant drugs include valaciclovir, penciclovir, famciclovir and vidarabine. However, even with chronic use, these drugs do not result in permanent clearance or long-term control. Moreover, issues such as drug resistance and safety concerns suggest that new and improved medication is urgently needed. Vaccines under development have also shown limited efficacy against herpes infections in humans. Thus the development of non-nucleoside HSV inhibitors with novel mechanisms of action is an important focus area of antiviral research. These factors underpin the need for the development of new anti-herpes drugs which not only target the wild type strains but also drug-resistant strains.[18-22]

The use of natural products in the manufacturing of drugs is an ancient and well-established practice. In the search for newer compounds showing potent antiviral activity, we have identified *Ficus arnottiana* plant extract as a potent agent against HSV infections.[23,24]

F. arnottiana commonly known as Indian Rock Fig and Paras Pipal in India belongs to family Moraceae. Traditionally the plant has being used for different therapeutic uses related to skin and genital disorders. Stem and bark part of the plant was used as astringent, aphrodisiac, demulcent, depurative and emollient. It was also useful against inflammation, diarrhoea, diabetes, burning sensation, leprosy, scabies, wounds and skin diseases. Recently it has been reported for its hypoglycemic, anti-oxidant and anti-ulcer activity.[25,26]

F. arnottiana plant extract was being developed as a topical cream formulation - Arnophyte® cream. It showed potent antiviral activity against both HSV-1 and HSV-2 in the *in vitro* and animal-models screening assays. This clinical study was planned to evaluate the efficacy and tolerability of Arnophyte® cream in subjects with early signs and symptoms of recurrent HSV-2.

METHODS

Preparation of investigational product

The investigational product was Arnophyte® cream, a topical formulation for external application. Arnophyte® cream contains 20% *F. arnottiana* plant extract as a potent agent against HSV-2 infection.

Study population

Forty eight patients were enrolled of which 40 patients completed the study (per protocol population). The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki, and the Ethics Committees reviewed the protocol and granted approval before the start of the study. All patients were provided written informed consent before study participation. Male and female patients of age between 18-60 years, with at least 1 herpes recurrence during the past 12 months and typically associated with ulcerative lesions, a recurrence that will lead to development of a lesion which undergoes prodrome (pain, burning, itching) vesicle, ulcer/soft crust and/or hard crust formation were included in the trial. Subjects using treatment or prevention with other systemic or topical antiviral agents; within 4 weeks prior to study drug administration or having any immunodeficiency disorders such as HIV and tuberculosis or receiving cancer chemotherapy were excluded from the study.

Study design and disposition

The study was an open label, phase 2, non-comparative study to evaluate the efficacy and tolerability of Arnophyte Cream in subjects with early signs & symptoms of recurrent HSV-2. The trail was conducted during 17th February 2015 to 23rd August 2015 at clinical site located at Worli, Mumbai, Maharashtra, India. The trail is registered with clinical trial registry of India and registration number is CTRI/2018/01/011171 (http://www.ctri.nic.in/).

The study drug was administered after allocation of patients to the two sites in the study and the safety evaluation at the baseline visit. Patients were advised to apply half FTU (fingertip unit) cream on affected area five times a day. The treatment was given for a period of

14 days. The efficacy of Arnophyte cream was evaluated on baseline/day1, day 2, 4, 7 and day 15. The drug accountability and treatment compliance was checked by recording in CRF for remaining or unused quantity of cream in terms of grams of the total unused medication.

Assessment

The primary outcome measured was assessment of reduction in pain between baseline, day 2, day 4, day 7 and day 15 using the visual analogue score (VAS). The changes in the Quality of Life Index for recurrent genital herpes (GHQoLr) was assessed on baseline, Day 4, Day 7 and Day 15; the physician's global assessment and patient's global assessment of the therapy was performed on baseline, day 2, day 4, day 7 and day 15. Signs and symptoms associated with HSV-2 and healing of the target lesion was assessed using a lesion score (lesions size and appearance) on baseline, day 2, day 4, day 7 and day 15. The safety parameters like CBC, SGPT, Sr. creatinine were measured on the screening day and day 15. Urine sample for urine routine and microscopy was also taken. Chest X-ray was also taken to check for tuberculosis.

Statistical analysis

Data was analyzed using SAS 9.4 and represented as Mean±SD or frequency (percentage) as per the type of data. Mean reduction in the lesion size by Chi square test, total lesion specific score by Univariate Test of Analysis, Wilks' Lambda or Pillai's Trace multivariate statistical Tests were used to compare the covariance between physicians global assessment (PhGA) and patients' global assessment (PtGA).

RESULTS

Patient demographic and other baseline characteristics

The patient's disposition is as per Table 1. The demographic data evaluation was done for total population. Percentage of females in study was 5.0%, whereas the percentage of males in study was 95.0%. The mean age in the study was 39.53±9.75 years. Similarly other baseline disease characteristics like average lesion size, number of recurrences n (%), VAS score, GHQoLr, lesion specific score, lesion specific score severity n (%), Physicians and patients global assessment are as per Table 2.

Table 1: Patients disposition (n=48).

Patient disposition	Treatment
Patients enrolled in study (ITT population)	48
Patients completing protocol (Per protocol population)	40
Patients discontinued	8
Patients discontinued at visit 1	2
Patients discontinued at visit 2	4
Patients discontinued at visit 3	2
Reason for discontinuation (n)	
Personal conflict/patient decision	0
Lost to follow-up	4
Physician decision	0
Non-compliance	2
Adverse event	2
Protocol violation or entry criteria not met	0
Lack of efficacy (per physician)	0
Lack of efficacy (per physician and/or patient)	0
Serious adverse event	0

Table 2: Baseline disease characteristics (n=40).

	Treatment group
Gender, N (%)	
Male	38 (95.0)
Female	2 (5.0)
Age (years)	
N	40
Mean	39.53
SD	9.756
Median	41.5
(Min, Max)	(20.00, 56.00)

Continued.

	Treatment group
Average lesion size	
N	40
Mean	1.31
SD	0.334
Median	1.5
(Min, Max)	(0.50, 2.00)
No of recurrences N (%)	
1st recurrence	21 (52.5)
2nd recurrence	16 (40.0)
3rd recurrence	3 (7.5)
Baseline VAS score	
N	40
Mean	60.7
SD	20.089
Median	70
(Min, Max)	(20.00, 86.00)
Baseline GHQoLr	
N	39
Mean	33.08
SD	3.351
Median	34
(Min, Max)	(22.00, 39.00)
Baseline lesion specific score	
N	40
Mean	14.55
SD	2.195
Median	15
(Min, Max)	(9.00, 18.00)
Baseline lesion specific score severity N (%)	
Patient having baseline severity ≥16.8	6 (15.0)
Patient having baseline severity ≥12	34 (85.0)
No of recurrences	
N	40
Mean	1.55
SD	0.639
Median	1
(Min, Max)	(1.00, 3.00)

Primary efficacy analyses

Visual analogue score (VAS) for pain was evaluated on baseline, day 2, day 4, day 7 and day 15. The mean VAS score at the baseline was 60.7 and at the day 15 visit it was reduced to 24.66, showing significant reduction in pain ANOVA probability ≤0.0001. The data indicates significant relief of pain by analyzing VAS score in between baseline visit to day 2, day 2 to day 4, day 2 to day 7 and day 7 to day 15. Complete pain reduction was noted in 6 patients (15%) on or before 6 days of treatment and 20 patients i.e. 50% patients were completely healed from pain.

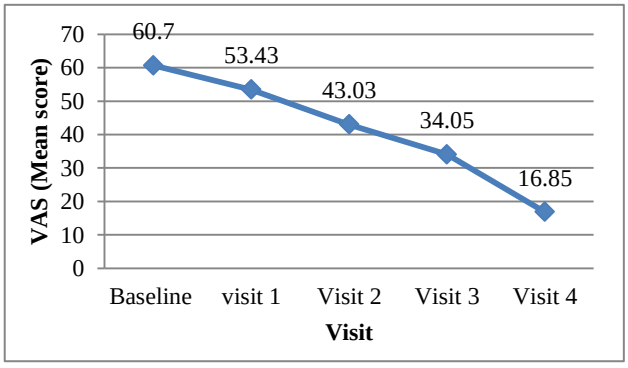

Figure 1: Line graph for measurement of improvement in pain from baseline to day 15.

Lesion size

During the treatment period the mean score of lesion size was 1.65 cm at baseline which reduced to 1.34 cm (±2.19 SD) at day 2 ($p<0.0001$). The mean size of lesion from day 4 was 1.03 cm (±0.33 SD), which was significantly reduced to 0.75 cm (±0.42 SD), ($p<0.0001$), on day 7 and this significantly reduced further to 0.34 cm (±0.44 SD), ($p<0.0001$), on day 15.

Lesion specific score

Lesion healing was evaluated using a lesion specific score where the target lesion was scored based on a Likert scale. The scale is used to record the severity of signs and symptoms (these include prodrome symptoms like itching, burning or tingling; local signs such as erythema, edema, vesiculation, erosion/ulceration and scabbing/crusting).

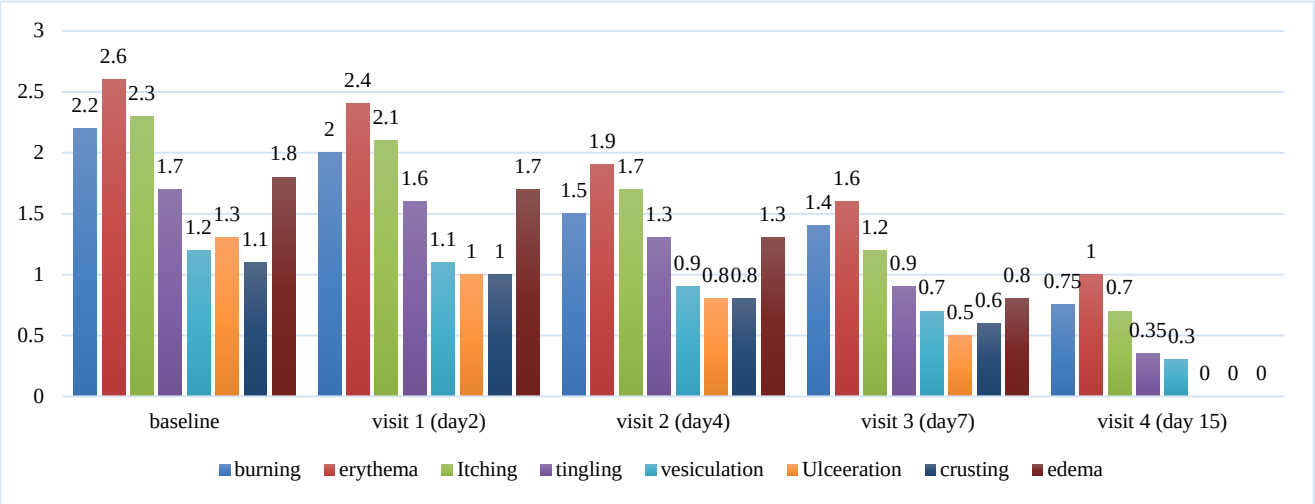

Figure 2: Mean lesion specific score.

Overall lesion specific score significantly reduced from 14.55±2.19 SD baseline to 4.53±2.75SD on day 15, $p<0.0001$, whereas tingling, vesiculation and ulceration were completely relieved. The symptoms like erythema, itching and burning showed good reduction i.e. >50%. There was no change found in the crusting of the lesion.

Improvement in the physical, social and mental domain by using GHQoLr

The results show that the physical symptoms were reduced significantly after 15 days as compared to the baseline 33±3.30 SD to 14.83±8.98, $p<0.0001$. Effect of treatment on daily activity domain of GHQoLr shows the improvement of daily activity, social domain, personal domain and the psychological domain.

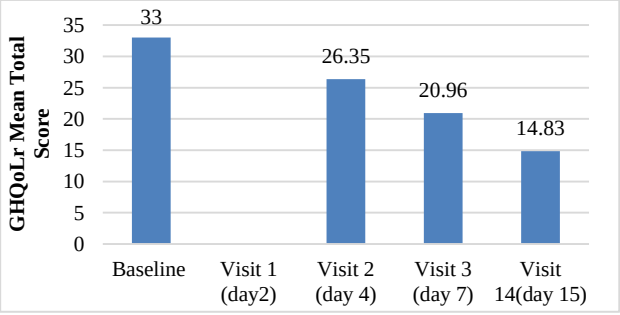

Figure 3: Improvement of quality of life by using GHQoLr.

Secondary efficacy assessment

Physicians and patients global assessment

The physicians' global assessment shows that the efficacy assessed by physician for the treatment shows that 23 (57.5%) patients showed healing from 75-99%. The patients' global assessment shows that the efficacy assessed by physician for the treatment shows that 29 (72.5%) patients showed healing from 75-99%.

Safety and adverse events

Treatment with the Arnophyte cream application showed overall 4 adverse events in 2 patients, the adverse events were common cold, diarrhea, flatulence and pyrexia. These adverse events were probably not related to study medication. No significant adverse events were observed during the study. No significant abnormality in the biochemical and hematological parameters were noted.

DISCUSSION

A feature of infection with the herpes virus group is the absence of virus elimination following clinical recovery. Once the virus enters the body, it passes through the skin to the nerves near the spine (neural ganglia), where it remains as a latent infection. When triggered, for example under conditions like stress or immunosuppression, the virus is transported back along

the neuron's axon to the surface of the skin where virus replication and shedding occurs, causing new sores. This is known as a recurrence. Recurrences are less severe and shorter than the first episode. In these cases only symptoms of prodrome and pain in the buttocks, thighs and genital areas may occur, and in some cases the lesions can be very mild and appear as red spots or mosquito bites.

Some of the clinically relevant drugs used during recurrence include acyclovir, valaciclovir (Valtrex), penciclovir, famciclovir (Famvir) and vidarabine. However, even with chronic use, these drugs do not result in permanent clearance. A recent review published in the Cochrane database of systematic reviews (2014) compared the effectiveness and safety of three oral antiviral drugs (acyclovir, famciclovir and valacyclovir) prescribed to suppress genital herpes outbreaks, showed that there was no evidence that the use of these antivirals reduced the number of patients with at least one recurrence as compared with placebo. These antivirals also have side effects like nausea, vomiting, diarrhea and headache.[27] Less frequently reported but more serious side effects may include mania, psychosis, hallucinations, confusion, liver enzyme abnormalities, renal failure, thrombocytopenia, leucopenia, and alopecia. Moreover, issues such as drug resistance especially in immunocompromised patients, suggest that the development of non-nucleoside HSV inhibitors with novel mechanisms of action is an important focus area of antiviral research.[28-30] These factors underpin the need for the development of new anti-herpes drugs which not only target the wild type strains but also drug-resistant strains.

Our topical product Arnophyte cream showed significant effect by reducing the pain associated with recurrence and the size of the lesion. Arnophyte cream has shown a good result in healing herpes lesions. The lesion specific score shows 17 (35.4%) patients almost healed on day 7 of the application. The symptoms like erythema, itching, tingling, burning, vesiculation, edema, ulceration and crusting were significantly reduced. Arnophyte application not only reduced the size of the lesion but also the duration of healing. The results are similar to the use of lysine to reduce the duration of outbreaks, and the use of zinc oxide cream to expedite healing of cold sores.[31,32] Clinical trials however have shown no changes in the rapidity of healing or viral shedding with topical application of a poly-l-lysine complex.[33] Use of other topical treatments such as Foscarnet was shown to reduce redness, blisters and swelling among men but not women. Foscarnet, and immune-modifiers has not shown much efficacy in reducing the recurrence of genital herpes infection.[34,35]

F. arnottiana based Arnophyte cream is known immunomodulatory and the efficacy of the application of the cream can be compared with the Canadian study describing the use of an ointment made of propolis, containing flavonoids which demonstrated faster healing of lesions compared to acyclovir and the placebo. But, similar to Arnophyte study for 40 patients, this was a small study of only 30 patients.[36]

The efficacy of the Arnophyte cream can be attributed to the standardized extract derived from an Indian herb *F. arnottiana* with potent anti-viral agent against both HSV-1 and HSV-2 infection. The Ficus species have previously demonstrated antibacterial, antifungal and antiviral activities. Phytochemical constitution studies of different species of Ficus (Moraceae) showed the presence of constituents including tannins, flavonols and flavonoids, terpenoids, coumarins, glycosides, esters, carbohydrates, serine protease, etc. Thus, these plants have great medicinal potential for the therapy of infection. Similarly, lesion healing can be due to its anti-oxidant and anti-ulcer activity. *Ficus arnottiana*, the fruit of plant contains β-sitosteroz, gluanol acetale and glucose, friedelin steroids, alkaloids, carbohydrates, tannins and phenols.[25,37]

The in-vitro antiviral activity observed in Arnophyte cream suggests that inhibition of viral replication occurs post viral adsorption phase and the virucidal effect of *F.arnottiana* against HSV-1 and HSV-2 virus was also determined using an assay at concentrations ranging from 25 to 400 µg/ml. The observed antiviral effect during the in-vitro study was comparatively better than that of ACV. *F.arnottiana* inhibited the penetration of HSV-1 and HSV-2 virus into Vero cells (host cells for growing virus). This inhibitory activity was significantly more potent than that of ACV (data not shown here).

The evidence based literature for *F.arnottiana*, In vitro and in vivo animal studies and in house studies which show virus replication inhibition, antiviral activity and good efficacy against both HSV-1 and HSV-2 infection; supports the outcome of this clinical study of Arnophyte cream.

CONCLUSION

The present study demonstrates the efficacy of Arnophyte® cream in treatment of signs and symptoms of recurrent genital herpes and improves the quality of life. Arnophyte® cream was well-tolerated and safe with no serious adverse events observed. The usage of this cream can be extended for managing primary cases of HSV infections, both HSV-1 and HSV-2, in addition to oral therapy. Also since it has shown benefits in the recurrent infection of HSV-2, it may find application in recurrent cases of HSV-1 even as a stand-alone therapy.

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Ethical approval: The study was approved by the institutional ethics committee

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