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The SILVER Study. Efficacy Of Topical Nitric-Zinc Complex Solution In The Treatment Of Resistant Warts: A Post-Marketing Evaluation.

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ABSTRACT:

BACKGROUND: The treatment of cutaneous viral warts caused by human papillomavirus (HPV) infection is often subject to local recurrence and a long clinical and treatment course. Our aim was to analyze real-life data on the treatment of difficult-to-treat warts from a multicenter post-marketing surveillance assessment on the efficacy, tolerability and safety of a commercially available nitric-zinc complex solution (NZCS).

METHODS: Dermatologists from 14 Italian centers completed a questionnaire about their clinical experience on treatment of “difficult-to-treat” warts, which included plantar, periungual, anogenital warts and warts on aesthetically sensitive areas. The questionnaire was designed to obtain detailed information on wart treatment and compare NZCS efficacy with previous treatments.

RESULTS: Of 106 questionnaires returned, 83 reported NZCS use; 67 had had previous treatments (23 cryotherapy, 2 electrocoagulation, 12 other topical application, and 30 combined treatment, such as laser, cryotherapy and/or electrocoagulation). NZCS had superior efficacy to that of previous treatments ($p < 0.0001$), resulting in 84.1% with a full or partial clearance (vs 44.8% for previous treatments), and had better local tolerability ($p < 0.0001$).

CONCLUSIONS: NZCS showed better efficacy and tolerability than other previous wart treatments.

INTRODUCTION

Warts are benign epithelial proliferations caused by skin or mucosal infection (Sterling, 2014, Bacelieri, 2015) with the human papillomavirus (HPV), of which 80 types have been characterized and several others reported (Sterling, 2014, Gibbs, 2006). Warts are common in childhood but can occur at any age. Small cohort observational studies have suggested that 5%-30% of children and young adults have warts (Sterling, 2014). Patients' quality of life can be impaired by the presence of warts, which may cause pain (eg. plantar warts may make walking painful), affect sexual activity (genital lesions may be physically or emotionally limiting), frustration due to persistence or recurrence, as well as social concern regarding others' negative judgement.

The HPV-associated warts are subdivided according to the area they affect: palmar wart (palm of hand, HPV type 2), plantar wart (soles of feet, HPV type 2), common wart (HPV types 1, 4, 27 and 57) and anogenital wart (AGW, HPV types 6 and 11) (Sterling, 2014, Gibbs, 2006). Anogenital warts are common, affecting 1% of sexually-active individuals (Sterling, 2014, Lacey, 2011), and highly infectious, with rates of transmission to partner of around 60% (Lacey, 2011). The HPV virus causes benign lesions on the skin and mucosa when it penetrates the epidermis, constituting several layers of epithelial tissue in the genital areas. The most typical symptoms are burning, pruritus and bleeding. Cancerous and pre-cancerous (penile, vulvar, and anal) lesions may coexist with AGWs (Lacey, 2011).

Warts may resolve spontaneously, but often require local epidermal destructive

treatments, which may be chemical, such as salicylic acid, physical, such as cryotherapy, virucidal, or antiproliferative agents. One of the standard wart treatments performed by dermatologists is cryotherapy, in which liquid nitrogen is applied to the wart to freeze it, although treatment approaches vary according to the anatomical site and the type of lesion. The procedure is very fast, taking less than a minute. This technique is sometimes painful, but it is inexpensive. The cure rate for wart cryotherapy is highly variable, and palmar warts have better cure rates than plantar warts (Sterling, 2014). In a randomized study, cryotherapy was shown to be more effective than salicylic acid for the treatment of hand warts, but salicylic acid was more effective than control (no treatment). Neither cryotherapy nor salicylic acid treatment appeared to be effective for plantar warts (Bruggink, 2010). A study carried out in U.K. podiatry practices on plantar wart clearance compared 12 weeks' treatment with salicylic acid against non-aggressive cryotherapy (1-2 sessions). Both treatments achieved a modest cure rate of only 14% (Cockayne, 2011). The results corroborated the lack of effectiveness of both salicylic acid and cryotherapy for treating plantar warts. A meta-analysis showed salicylic acid (49% mean cure rate) to be more effective than placebo (23% mean cure rate) (Kwok, 2012).

Cohort and case-control studies observed CO₂ laser therapy to be a good ablative approach, yielding cure rates of up to 75% for resistant common warts. However, pain, bleeding, and reduced function are common side effects that need to be considered (Hruza, 2002). Pulsed dye lasers are a non-ablative option for genital and extragenital warts: efficacy studies have reported cure rates of 48% to 93% for different types of warts after 2 or 3 treatments (Borovoy, 1996, Goldman, 1999). Electrocoagulation is a common

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procedure in the treatment of primary multiple and widespread AGWs in some countries (Silvera, 2014). Immunological therapies are another effective option for AGWs, and the topical application of immune-stimulating molecules, as such as imiquimod, or the administration of HPV vaccines, have been shown to be effective in the treatment and prevention of AGWs.

Treatment can be very painful, particularly for plantar warts, and combined treatments are often required. Some warts are difficult to treat due to their location, for example, periungual warts, which are close to the unguis matrix. Recurrence is another problem, which leads to treatment drop-out. Nitric-zinc complex solution (NZCS) appears to be a good treatment option for very resistant warts; the topical solution contains nitric acid, zinc, copper and an organic acid with a caustic effect that causes “mummification”, protein denaturation and coagulation of the wart (Cusini, 2015; Rozas-Muñoz, 2019).

The present study aimed, first, to collect epidemiological data on the treatment of difficult-to-treat warts, which included plantar, periungual, genital warts and warts on aesthetically sensitive areas, to evaluate the current impact of this condition in the dermatological field, and second, to establish the efficacy and tolerability of NZCS compared with previous treatments. Difficult-to-treat warts referred to palmoplantar, periungual, and external genital warts that had relapsed after previous treatment.

METHODS

A questionnaire was developed and sent to 14 Italian dermatology centers. Instructions to dermatologists were to complete one questionnaire for each patient who

had difficult-to-treat warts. The questionnaire contained items on patient demographics, predisposing factors, wart location/type, number, duration, the presence of persistent or recurrent warts, previous treatment type, treatment efficacy (response) and tolerability. Complete response was established as 100% clearance, partial response as >50%, and no response as a <50% reduction in the diameter of the lesion.

Of 106 questionnaires returned, 23 were excluded from the statistical analysis on NZCS efficacy because the patients did not receive this treatment (NZCS, ISDIN SA). The NZCS treatment consisted of topical application of the solution (ampoules of 0.10 mL, using the capillary) directly to the wart, every 2 weeks. The results from patients who received NZCS treatment as their first line or secondary treatment option (n=83) were compared with the data obtained from other previous treatment modalities (n=67).

Statistical analyses

Descriptive analysis was performed for all variables. Continuous variables were described as the number of valid cases, mean, standard deviation, and 25th and 75th percentile (P25-P75). Categorical variables were described for each category as absolute and relative frequency over the total valid values (N). ANOVA, chi-squared, or Fisher exact test were used as applicable. Continuous variables were analyzed with Student t-test, ANOVA or Mann-Whitney U test as applicable. The level of significance was set at 0.05 ($p < 0.05$).

RESULTS

Demographic Data

Patients (n=83) were equally distributed regarding gender (51.8% male, 48.2% female), and the mean age was 27.71 ± 15.76 years. Thirteen patients were younger than 12 years (15.9%), 45.1% were between 12-30 years and 39.0% were older than 30 years (Table 1).

Most patients (81.9%) had no predisposing factors for cutaneous warts; 18.1% had predisposing factors, which included immunodeficiency, HIV positive status, atopy, nail biting, attending school, or swimming.

Most of the difficult-to-treat warts were palmoplantar (43.4%), AGW (24.1%) or periungual warts (20.5%); there was a low incidence of combined wart locations (7.2%) or recurrent warts (4.8%). The mean duration of difficult-to-treat warts was 1.25 ± 1.80 months, maximum 12 months.

Patients had a mean of 4 simultaneous lesions (4.32 ± 6.61) located mainly on the hands (36.2%) and feet (26.5%). Other areas were also affected (24.1%), sometimes more than one area simultaneously (combinations, 12%). Only one patient (1.2%) had lesions on the face (Table 1).

Questionnaires detailing previous treatments (n=67) reported that the mean number of previous treatments was 3.52 ± 3.66 . Previous treatments were: combined treatments (44.8%), cryotherapy alone (34.3%), topical treatment alone (17.9%), and electrocoagulation alone (3.0%). None had laser therapy alone. Of the patients who had

received combined treatments (n=30), 17 had cryotherapy + topical treatment, 7 had electrocoagulation + topical treatment, 3 had cryotherapy + electrocoagulation, 1 had cryotherapy + laser, 1 had cryotherapy + electrocoagulation + topical treatment, and 1 had cryotherapy + electrocoagulation + laser + topical treatment (Table 2). Overall, prior treatments were completely effective in 3.0%, partially effective in 41.8%, and not effective in 55.2%; tolerability was good in 34.3 %, moderate in 49.3%, and poor in 16.4% (Figure 1a,b).

The mean number of NZCS applications was 2.16 ± 1.07 . Data were missing for 1 patient, and of the remaining 82 treated with NZCS, 20.7% had complete response, 63.4% had partial response, and 15.9% had no response. Tolerability was good in 69.5%, moderate in 22.0%, and poor in 8.5%. Compared to overall previous treatments, NZCS had a significantly superior efficacy ($p < 0.0001$) (Figure 1a) and tolerability ($p < 0.0001$) (Figure 1b).

Upon analysis of the different types of wart (palmoplantar, periungual, AGW and recurrent warts), differences in NZCS efficacy were observed between patients with (n=41) and without (n=41) palmoplantar warts ($p = 0.02$). NZCS was more effective in those without palmoplantar warts (complete response in 22.0% of those with palmoplantar warts, 19.5% of those without, partial response in 51.2% with, 75.6% without). In both groups, NZCS had similar tolerability ($p = 0.378$).

NZCS efficacy also differed between patients with (n=23) and without (n=59) periungual warts ($p = 0.01$) in that most of the patients with periungual warts (91.3%) had

partial response (vs 52.5% for non-periungual warts), while only 4.3% had complete response (vs 27.1% for non-periungual warts).

The efficacy and tolerability were similar between patients with (n=20) and without (n=62) AGW ($p>0.05$), with total response in 30.0% and partial response in 65.0% of those with AGW.

Most of the patients with recurrent warts (n=7) treated with NZCS (n=83) had complete (28.6 %) or partial (71.5%) resolution.

On analysis of the different areas affected (hands, feet, face and other), there was a similar efficacy ($p=0.24$) and tolerability ($p=0.07$) in patients with (n=38) and without (n=44) hand lesions. NZCS treatment resulted in total (18.4%) or partial (73.7%) resolution in patients with hand lesions (92.1%). Differences in efficacy were also found between patients with (n=29) and without (n=53) foot lesions ($p=0.04$), but tolerability was similar between these two groups ($p=0.36$). Only 1 subject had facial warts, and the lesions resolved completely.

DISCUSSION

The dermatology community is well aware of the challenges involved in the treatment of common warts and AGWs, which remains unsatisfactory due to the partial effectiveness of most approaches. Recurrence rates are also high and constitute a significant problem.

The present study demonstrates that NCZS had superior efficacy and

tolerability than previous wart treatments (which included cryotherapy, topical treatment, electrocoagulation, and laser therapy, in various combinations). The warts treated in this study were mostly palmoplantar warts, followed by periungual and anogenital warts.

Many of the treatments for difficult-to-treat warts, such as cryotherapy, curettage or salicylic acid have been shown to be unsatisfactory (Jablonska, 1998). A previous study found that patients with difficult-to-treat warts or AGWs who were treated with NZCS achieved complete cure (90%) after 1-4 sessions, and the solution was well-tolerated by the patients (Cusini, 2014). The author postulated that NZCS was more effective than cryotherapy in destroying HPV DNA because of the nitrates formed after topical application of the product (Viennet, 2013).

Compared with salicylic acid, NZCS presents some advantages: salicylic acid needs a daily application whereas NZCS can be applied every 2 weeks. Contact allergy to the excipients of salicylic acid has also been reported (Sterling, 2014). In addition to causing scarring and burning, topical salicylic acid, cryotherapy, TCA (trichloroacetic acid), and podophyllotoxin also have high recurrence rates. Imiquimod therapy is a highly efficacious treatment alternative, but it carries with it several disadvantages, including its cost and a more severe cutaneous reaction associated with crusting and pain.

Nitric-zinc complex solution has previously been demonstrated to be effective in the treatment of palmar, plantar and periungual warts in 100% of treated lesions after 2-3 sessions (Cusini, 2014; Rozas-Muñoz, 2019). The authors also reported NZCS was well tolerated with no serious adverse events and no pain reported. A recent prospective study in 11 immunocompetent patients with resistant AGWs not cured by imiquimod or

cryotherapy found complete resolution of warts in all patients at 15 days, with recurrence in only 1 patient at a different site from that treated (Kelati, 2018).

The present study demonstrates that topical NZCS had a higher efficacy rate than that reported for different previous treatments. Of the patients who had previous treatment, 34.3% had received cryotherapy. Cryotherapy is painful, can cause blistering, and has a long duration (up to 4 months). Hypopigmentation or hyperpigmentation may also occur, particularly in patients with darker skin types. In addition, it has modest efficacy (Sterling, 2014): often a second or third freeze cycle is required at each session, and sessions are repeated every 1 to 2 weeks, while recurrence rates range from 38% to 73% at six months (Karnes, 2014).

The estimated treatment cost, based on brand name drugs, for all available AGW treatments is high. A study reported that podophyllin was the most expensive treatment, followed by imiquimod, TCA or BCA (bichloroacetic acid), cryotherapy, vaccination, podofilox, sinecatechins, electrosurgery, and surgical excision (Karnes, 2014).

Although electrocoagulation represented just 3% of previous treatments in the present study, it worth mentioning that, as is the case with other destructive methods, this treatment seems to be less effective for recurrent genital warts when used alone than when combined with other treatments (Ibishev 2013).

It was previously reported that papillomavirus DNA can be present in the smoke derived from plantar warts treated with electrocoagulation or CO₂ laser therapy, which represents a risk of papillomavirus contamination for laser operators (Sawchuk,

1989). Although this risk is reduced by use of masks and smoke evacuation systems, the simplicity of the NZCS administration method represents a major advantage in terms of safety. Furthermore, features such as the low number of applications required make NZCS suitable for use in the treatment of difficult warts, particularly in the case of AGWs or warts in children.

In the present study, nitric-zinc complex solution, or NZCS, containing organic and inorganic acids, has been shown to be an effective and well-tolerated treatment for recurrent palmoplantar, periungual, and anogenital warts, corroborating the results observed in previous studies. A limitation of our study is the fact it was impossible to control how many previous warts patients had before attending the dermatology centers. Future studies are still required to explain the mechanisms of resistance of recurrent warts.

CONCLUSION

NZCS had better efficacy and tolerability than other previous wart treatments. NZCS could be considered a less invasive, less painful, cheaper, and easy-to-use effective treatment strategy, requiring few applications, for difficult-to-treat warts, including periungual, facial, and external genital warts (condylomas), with no serious adverse effects. It is suitable for use in adults and children.

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FIGURE and TABLE LEGENDS:

Table 1. Baseline characteristics.

Table 2. Patients' previous wart treatments.

Figure 1.

Efficacy of nitric-zinc acid complex solution compared to previous treatments ($p < 0.0001$)
(a). Tolerability of nitric-zinc acid complex solution compared to previous treatments.
Statistical analysis comparing previous treatments and NZCS treatment showed a statistically significant difference ($p < 0.0001$) (b).

Table 1. Baseline characteristics

Baseline characteristics	n=83	Patients
Sex	Male	43 (51.8%)
	Female	40 (48.2%)
Age	Mean \pm SD	27.71 \pm 15.76 years
	<12 years	13 (15.9%)
	12-30 years	37 (45.1%)
	>30 years	32 (39%)
	n missing	1
Types of warts	Palmoplantar	36 (43.4%)
	AGW	20 (24.1%)
	Periungual	17 (20.5%)
	Combined	6 (7.2%)
	Recurrent warts	4 (4.8%)
Treatment duration of difficult-to-treat warts	Mean \pm SD	1.25 \pm 1.80 months
Number of warts per patient	Mean \pm SD	4.32 \pm 6.61 lesions
Location of warts treated	Hands	30 (36.1%)
	Feet	22 (26.5%)
	Other	20 (24.1%)
	Combination	10 (12%)
	Face	1 (1.2%)
Data are shown as mean \pm standard deviation (SD) or as n (%) when appropriate.		

Table 2. Patients' previous wart treatments.

Previous treatments	n= 67	Patients
Cryotherapy		23 (34.3%)
Topical treatment		12 (17.9%)
Electrocoagulation		2 (3%)
Combined		30 (44.78%)
	Types of combinations:	
	Cryotherapy + topical treatment	17
	Electrocoagulation + topical treatment	7
	Cryotherapy + electrocoagulation	3
	Cryotherapy + laser	1
	Cryotherapy + electrocoagulation + topical treatment	1
	Cryotherapy + electrocoagulation + laser + topical treatment	1
Data are shown as n (%) or n when appropriate.		





