

Treatment of warts with topical cidofovir in a pediatric patient

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Abstract

Cidofovir is an antiviral nucleotide analogue with relatively new treatment capacities for dermatological conditions, specifically verruca vulgaris caused by human papilloma virus infection. In a 10-year old boy with severe verruca vulgaris recalcitrant to multiple therapies, topical 1% cidofovir applied daily for eight weeks proved to be an effective treatment with no adverse side effects. This case report, in conjunction with multiple published reports, suggests that topical 1% cidofovir is a safe and effective treatment for viral warts in pediatric patients.

Keywords: cidofovir, verruca vulgaris, human papilloma virus

Introduction

Cidofovir was the first nucleotide analogue approved for clinical use. It reacts strongly against a variety of DNA viruses by competitively inhibiting DNA polymerase and blocking viral DNA synthesis and replication [1]. Although it was initially intended to treat cytomegalovirus (CMV) retinitis in patients with AIDS, recent findings suggest evidence that topical cidofovir is effective in treating a range of dermatologic conditions, including verruca vulgaris caused by human papilloma virus (HPV) infection.

Since HIV infected individuals are at an increased risk for HPV infection, extensive research has examined the impact of cidofovir use in immunocompromised patients. An experimental study found that 1-3%

topical cidofovir is effective in treating HPV lesions and molluscum contagiosum in adult patients with HIV/AIDS [2]. Case reports have also found topical cidofovir to effectively treat anogenital squamous cell carcinoma (SCC), bowenoid papulosis, condyloma acuminatum, Kaposi sarcoma, and HSV-II in adult patients with HIV/AIDS [3]. Cidofovir has experimentally been shown to be effective in treating genital condyloma acuminata in adult immunocompetent patients [4] and in a pediatric case [5].

Cidofovir has also been used in pediatric patients to cure verruca vulgaris recalcitrant to traditional treatment therapies. There have been several reports that topical 1-3% cidofovir cream applied once or twice daily is effective in treating verruca vulgaris with no systemic side effects and low rates of recurrence in immunocompetent children [6-8], as well as in immunocompromised children [9, 10]. These studies have used topical cidofovir to treat periungual, plantar, and anogenital verrucae as well as verrucous lesions on the hands and lips. It has been suggested that 1 to 3% concentration gives the best results on cutaneous lesions when applied twice daily. Topical cidofovir should be applied once daily, every other day, on delicate areas such as the lips, gums, and genitalia [2].

Topical cidofovir has been shown to be a relatively safe treatment, with the most common side effect being local irritation [8-9]. However, a single case of reversible nephrotoxicity related to topical cidofovir has been reported in a 28-year old immunosuppressed patient with chronic renal



Figure 1. Pre-treatment photo showing numerous verrucae on the dorsal hands and right palmar hand.



Figure 2. Pre-treatment photo with several verruca over the columella of the nose and left lateral canthus.

insufficiency. In this case, 4% cidofovir compounded in propylene glycol was applied on abraded skin [11]. Therefore, it is advised not to apply topical cidofovir

to open wounds or in a concentration above 3%, especially in chronic renal disease patients.

Case Synopsis

A 10-year-old healthy boy, with no history of immunosuppression, presented to clinic with over 50 verrucous papules distributed diffusely over the hands and face. The patient had periungual warts on nearly all fingers of both hands, multiple larger papules and plaques on the palmar surface, and a larger plaque at the base of his right dorsal thumb (**Figure 1**). On the face, he had two white filiform papules over the columella and one near the left lateral canthus (**Figure 2**). His mother reported that the warts first appeared three years prior on the hands and later spread to the face. Prior to



Figure 3. Post-treatment photo with resolution of verrucae over the right dorsal hand and right palmar hand.



Figure 4. Post-treatment photo with resolution of verrucae over the face.

presentation, the patient tried various topical formulations of salicylic acid (ranging from 17 to 40%) without significant success. In clinic, he was first treated with intralesional *Candida albicans* antigen. The patient received two injections of 0.15ml *Candida* antigen each into two representative palmar lesions after the first visit. This was repeated over two more sessions, spaced three weeks apart, for a total of 0.9ml of intralesional *Candida* antigen. The patient was also started on oral cimetidine 600mg twice daily, after the first visit. Four weeks after the third and final session of intralesional *Candida* injection, the patient still had no appreciable response and was prescribed compounded topical 1% cidofovir cream. A 1% formulation was chosen as it was the preferred compounded strength at the mail order Philadelphia Chemistry Rx Pharmacy; they were able to provide a 15g tube for \$225. No additional treatment modalities, such as topical salicylic acid were prescribed concurrently. Eight weeks after initiation of topical 1% cidofovir, applied once daily, with complete use of a single 15g tube of compounded

medication, the patient returned for follow up and was noted to have near-complete resolution of all verrucae (**Figures 3, 4**). The patient had scattered hypopigmented macules at the site of resolved lesions on the dorsal hands but reported no systemic side effects and was overall very pleased with treatment. Six months after treatment there has been no report of recurrence.

Case Discussion

From a literature review performed of the available published reports in which topical cidofovir was used to treat warts, complete improvement was seen in 171 of 297 cases in immunocompetent patients and 44 of 59 cases in immunocompromised patients (**Tables 1, 2**). Similarly, partial improvement was seen in 89 of 297 cases in immunocompetent patients and 8 of 59 cases in immunocompromised patients (**Tables 1, 2**).

As evidenced in this case, topical 1% cidofovir applied once daily for eight weeks proved to be an effective treatment of diffuse verrucae vulgaris in a child recalcitrant to multiple treatments including salicylic acid, oral cimetidine, and intralesional *Candida* antigen. This case adds to the growing body of evidence of the therapeutic efficacy of topical cidofovir for viral warts in both children and adults. As verruca vulgaris is particularly common in children and can prove difficult to treat, it is important to continue to investigate alternative treatment therapies. As the concentration and dosing schedule varies in published cases, clinical trials should be conducted to determine the ideal concentration of treatment and application

Table 1. Non-Immunocompromised patients treated with topical cidofovir.

	Complete improvement *	Partial improvement**
Aggregate Case reports [5, 27, 31, 32]	7/8	0/8
Aggregate Retrospective studies [6-8, 12-15]	146/243	66/243
Experimental studies		
Snoeck et al., 2001 [4]	9/19	7/19
Coremans et al., 2003 [20] (37% of patients were immunocompromised)	9/27	16/27

Table 2. Immunocompromised patients treated with topical cidofovir.

	Complete improvement*	Partial improvement**
Aggregate Case reports and Case series [9-11, 16, 18, 19, 22-26, 28, 30]	15/16	1/16
Prospective studies [17]	4/10	3/10
Aggregate Retrospective studies [7, 15]	3/4	0/4
Experimental studies		
Calista, 2000 [2]	13/13	0/13
Matteeli et al., 2001 [21]	7/12	4/12
Toustous-Trellu et al., 2004 [29]	2/4	0/4

Note: Topical cidofovir treatment concentrations ranged between 0.5% and 4%. Treatment length ranged between one and 40 weeks.

*Complete improvement is defined as a total disappearance of all lesions (including through multiple courses of the same treatment).

** Partial improvement is defined as a reduction in the number and/or size of the lesions but without complete disappearance (by the end of the examined study).

schedule. Consistent with our case, treatment should be stopped if there are no results after 10 -12 weeks, as improvement is usually seen within this amount of time [12].

Conclusion

In the United States, topical cidofovir is not a routinely available medication and must be compounded prior to use, which leads to barriers in

obtaining the medication for many patients. However, successful treatments outcomes, such as that seen in this patient, may help contribute to its establishment as a routinely available, safe, accepted treatment of verruca vulgaris.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

- Zabawski EJ, Cockerell CJ. Topical and intralesional cidofovir: A review of pharmacology and therapeutic effects. *J Am Acad of Dermatol.* 1998;39:741-5. [PMID: 9810890].
- Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. *J Eur Acad of Dermatol Venereol.* 2000;14:484-8. [PMID: 11444271].
- Toro JR, Sanchez S, Turiansky G, Blauvelt A. Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox. *Dermatol Clin.* 2003;21:301-9. [PMID: 12757253].
- Snoeck R, Bossens M, Parent D, Delaere B, Degreef H, Van Ranst M, Noël JC, Wulfsohn MS, Rooney JF, Jaffe HS, De Clercq E. Phase II Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Cidofovir Topical Gel for the Treatment of Patients with Human Papillomavirus Infection. *Clin Infect Dis.* 2001;33:597-602. [PMID: 11477525].
- Calisto D, Arcangeli F. Topical cidofovir for condylomata acuminata of the genitalia in a 3-year-old child. *J Am Acad Dermatol.* 2003;49:1192-3. [PMID: 14639419].
- Padilla España L, Del Boz J, Fernández Morano T, Arenas Villafranca J, de Troya Martín M. Topical cidofovir for plantar warts. *Dermatol Ther.* 2013;27:89-93. [PMID: 24433270].
- Field S, Irvine AD, Kirby B. The treatment of viral warts with topical cidofovir 1%: our experience of seven paediatric patients. *Br J Dermatol.* 2009;160:223-4. [PMID: 19067689].
- Fernández-Morano T, del Boz J, González-Carrascosa M, Tortajada B, de Troya M. Topical cidofovir for viral warts in children. *J Eur Acad of Dermatol Venereol.* 2011;25:1487-9. [PMID: 21261749].
- Tobin AM, Cotter M, Irvine AD, Kirby B. Successful treatment of a refractory verruca in a child with acute lymphoblastic leukaemia with topical cidofovir. *Br J Dermatol.* 2005;152:386-8. [PMID: 15727669].
- Henrickson SE, Treat JR. Topical Cidofovir for Recalcitrant Verrucae in Individuals with Severe Combined Immunodeficiency After Hematopoietic Stem Cell Transplantation. *Pediatr Dermatol.* 2016;34:24-5. [PMID: 27699886].
- Bienvenu B, Martínez F, Devergie A, Rybojad M, Rivet J, Bellenger P, Morel P, Gluckman E, Lebbé C. Topical use of cidofovir induced acute renal failure. *Transplantation.* 2002;73:661-2. [PMID: 11889450].
- Padilla España L, Del Boz J, Fernández-Morano T, Escudero-Santos I, Arenas-Villafranca J, de Troya M. Recalcitrant warts and topical cidofovir: Predictive factors of good response. *J Eur Acad of Dermatol Venereol.* 2015;30:1218-20. [PMID: 25864554].
- Padilla España L, Del Boz J, Fernández-Morano T, Arenas-Villafranca J, de Troya M. Successful treatment of periungual warts

- with topical cidofovir. *Dermatol Ther.* 2014;27:337-42. [PMID: 25081902].
14. Fernández-Morano T, Del Boz J, Frieyro-Elichegui M, Repiso JB, Padilla-España L, de Troya-Martín M. Tratamiento de verrugas anogenitales con cidofovir tópico [Treatment of anogenital warts with topical cidofovir]. *Enferm Infecc Microbiol Clin.* 2013;31:222-6. [PMID: 23182242].
 15. Gupta M, Bayliss SJ, Berk DR. Topical Cidofovir for Refractory Verrucae in Children. *Pediatr Dermatol.* 2012;30:131-4. [PMID: 23013353].
 16. Cleary A, Watson R, McMahan CJ. Successful treatment of refractory cutaneous warts using topical 3% cidofovir in a child after heart transplant. *J Heart Lung Transplant.* 2014;33:971-2. [PMID: 24726426].
 17. Orlando G, Fasolo MM, Beretta R, et al. Intralesional or topical cidofovir (HPMPC, VISTIDE) for the treatment of recurrent genital warts in HIV-1-infected patients. *AIDS.* 1999;13:1978-80. [PMID: 10513659].
 18. Kralund HH, Broesby-Olsen S, Bistrup C, Lorentzen HF. Substantial Effect of Topical Cidofovir 1% on Recalcitrant Warts in a Renal-Transplanted Adolescent: A Case Report. *Transplantation.* 2011;91:e52-4. [PMID: 21436652].
 19. Davis MD, Gostout BS, cRMM, Persing DH, Schut RL, Pittelkow MR. Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. *J Am Acad Dermatol.* 2000;43:340-3. [PMID: 10901717].
 20. Coremans G, Margaritis V, Snoeck R, Wyndaele J, Clercq ED, Geboes K. Topical Cidofovir (HPMPC) Is an Effective Adjuvant to Surgical Treatment of Anogenital Condylomata Acuminata. *Dis Colon Rectum.* 2003;46:1103-9. [PMID: 12907906].
 21. Matteelli A, Beltrame A, Graifemberghi S, et al. Efficacy and Tolerability of Topical 1% Cidofovir Cream for the Treatment of External Anogenital Warts in HIV-Infected Persons. *Sex Transm Dis.* 2001;28:343-6. [PMID: 11403192].
 22. Cha S, Johnston L, Natkunam Y, Brown J. Treatment of verruca vulgaris with topical cidofovir in an immunocompromised patient: a case report and review of the literature. *Transpl Infect Dis.* 2005;7:158-161. [PMID: 16390407].
 23. Husak R, Zouboulis C, Sander-Bahr C, Hummel M, Orfanos C. Refractory human papillomavirus-associated oral warts treated topically with 1-3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol.* 2005;152:590-1. [PMID: 15787847].
 24. Mariño AT, González JC, Bobo MI, Rodríguez FA. Cidofovir tópico para el tratamiento de verrugas plantares [Topical cidofovir as a treatment for plantar warts]. *Farm Hosp.* 2010;34:48-9. [PMID: 20144824].
 25. Martinelli C, Farese A, Mistro AD, Giorgini S, Ruffino I. Resolution of recurrent perianal condylomata acuminata by topical cidofovir in patients with HIV infection. *J Eur Acad Dermatol Venereol.* 2001;15:568-9. [PMID: 11843219].
 26. Socio GVL, Simonetti S, Rosignoli D, Minga P, Tomassini GM, Baldelli F. Topical cidofovir for severe warts in a patient affected by AIDS and Hodgkins lymphoma. *Int J STD AIDS.* 2008;19:715-6. [PMID: 18824628].
 27. Zabawski EJ. Treatment of verruca vulgaris with topical cidofovir. *JAMA.* 1997;278:1236. [PMID: 9333263].
 28. Das BB, Anton K, Knox L, Jarin J, Sue PK. Successful treatment of giant condyloma in a pediatric heart transplant recipient with topical cidofovir. *Transpl Infect Dis.* 2018;20:e12989. [PMID: 30184307].
 29. Toutous-Trellu L, Hirschel B, Piguet V, Schiffer V, Saurat J-H, Pechère M. Traitement par cidofovir topique d'infections cutanées à papillomavirus humain, poxvirus et Herpes simplex virus chez des malades séropositifs pour le VIH. [Treatment of cutaneous human papilloma virus, poxvirus and herpes simplex virus infections with topical cidofovir in HIV positive patients]. *Ann Dermatol Venereol.* 2004;131:445-9. [PMID: 15235531].
 30. Schürmann D, Bergmann F, Temmesfeld-Wollbrück B, Grobusch MP, Suttrop N. Topical cidofovir is effective in treating extensive penile condylomata acuminata. *AIDS.* 2000;14:1075-6. [PMID: 10853999].
 31. Hengge UR, Tietze G. Successful treatment of recalcitrant condyloma with topical cidofovir. *Sex Transm Infect.* 2000;76:143. [PMID: 10858720].
 32. Stragier I, Snoeck R, Clercq ED, Oord JJVD, Ranst MV, Greef HD. Local treatment of HPV-induced skin lesions by Cidofovir. *J Med Virol.* 2002;67:241-5. [PMID: 11992585].