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Topical therapies for the treatment of anal high-grade squamous intraepithelial lesions

Christina Megill, PA-C and

Division of Infectious Diseases, Weill Cornell Medicine 53 W. 23rd St. 6th Floor, New York, NY 10010, 212-746-7204 (phone), 212-746-7203 (fax)

Timothy Wilkin, M.D., MPH [Associate Professor of Medicine]

Division of Infectious Diseases, Weill Cornell Medicine 53 W. 23rd St. 6th Floor, New York, NY 10010, 212-746-7204 (phone), 212-746-7203 (fax)

Abstract

Anal cancer may be prevented by treating anal high-grade squamous intraepithelial lesions (HSIL). Ablative therapies are the most commonly used treatments, but they may not be appropriate for all patients including those with extensive HSIL or bleeding diatheses. Researchers have studied topical therapies for human papillomavirus related lesions including anal HSIL. These therapies include patient-applied 5-fluorouracil, imiquimod and cidofovir, and provider-applied trichloroacetic acid. This review will discuss literature supporting efficacy of these products, which is based mainly on case series with few controlled trials having been conducted. Side effects are common with patient-applied topical therapy often requiring dose reduction and medication to treat pain. However, treatment discontinuations are infrequent. This review will also discuss some approaches to the use of these products in clinical practice.

Keywords

Imiquimod; Fluorouracil; Cidofovir; Trichloroacetic acid; Anal dysplasia

Introduction

Anal cancer is preceded by high-grade intraepithelial lesions (HSIL) and causally linked to persistent infection with high-risk or oncogenic strains of human papillomavirus (HPV). The rates of anal cancer are markedly elevated in HIV-infected people, particularly men who have sex with men¹. Anal HSIL is found in up to 50% of HIV-infected men and 25% of HIV-infected women^{2, 3}. Treating anal HSIL has been proposed as a strategy for reducing rates of anal cancer in HIV-infected adults and a randomized clinical trial is underway that will test this hypothesis.

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The most commonly used treatments for anal HSIL are ablative procedures such as hyfrecation/fulguration and infrared coagulation. These treatments are typically performed in the office setting. These procedures are effective, but may require multiple treatments and have potential post-procedure complications. Infrared coagulation can eliminate a given lesion 64-81% of the time, but anal HSIL may develop at other untreated sites in up to 70% of patients⁴⁻⁶. Ablation may be inappropriate for patients with extensive or circumferential disease, and may be inappropriate for patients receiving anticoagulants or with bleeding diatheses. Treatment of anal HSIL in HIV-infected adults is difficult as anal HSIL in this group is more extensive and responds less well to ablative therapy as compared to HIV-uninfected groups⁷.

Topical therapies are an alternative approach to ablative treatments. There are no FDA-approved topical therapies for anal HSIL, but based on similarities between the pathophysiology of other genital squamous cell intraepithelial lesions and anal HSIL, patient-applied imiquimod, 5-fluorouracil, and cidofovir have been used for topical treatment of peri-anal and intra-anal HSIL. Provider-applied trichloroacetic acid is also a viable treatment option. There are few controlled clinical trials to determine efficacy of treatments and fewer studies that compare treatment modalities. The current approach to treatment of anal HSIL using topical therapy is informed mainly by case series, small non-randomized trials and inference from studies of other HPV-associated lesions. (Table 1) This review will discuss existing data and possible uses for these treatments.

5-fluorouracil (5FU)

Topical treatment with 5-fluorouracil (5FU) was first reported in 1962 for treatment of skin cancers following a report that systemic 5FU induced regression of keratosis⁸. 5FU is a pyrimidine analog made by fluorination of uracil on position 5 of the pyrimidine ring. Its principle mechanism of action is to inhibit DNA synthesis by blocking the conversion of uracil deoxyribonucleotide to thymine deoxyribonucleotide⁹. This conversion creates a thymine deficiency resulting in a DNA deficiency, thus leading to disordered function that results in the inability of cells to replicate. A secondary effect of 5FU is direct interference with RNA synthesis and function, inhibiting the incorporation of uracil into RNA by competing with uracil-active enzymes. 5FU's most marked affect is on rapidly proliferating tissues and is commercially available as 1, 2, and 5% 5FU topical cream or gel. The most commonly used concentration for treatment of anal HSIL is 5%. It causes erythema and edema followed by erosion, ulceration and necrosis when applied topically to a neoplasm. It has been shown to preferentially treat neoplasms with only an inflammatory response on adjacent healthy skin.

Topical 5FU has been used since the 1970s to treat female lower genital tract disease caused by HPV¹⁰⁻¹³. There are limited data and a few randomized placebo controlled trials evaluating 5FU for genital warts; a Cochrane review suggests that there is evidence for a therapeutic effect against genital warts¹⁴. A randomized study evaluated 5FU 5% as prophylactic therapy to prevent recurrence of cervical HSIL following loop electro-excision procedure in HIV-infected women¹¹. Recurrence of cervical HSIL in the 5FU group was 28% compared to 47% in the observation group.

There are limited reports of 5FU 5% specifically for treatment of anal lesions. In one study evaluating treatment of patients with perianal HSIL, 7 of 8 patients treated with topical 5FU 5% cream applied twice weekly for 16 weeks had no evidence of perianal HSIL on follow-up biopsies at 12 months post-treatment¹⁵. Richel and colleagues reported an open-label study of 46 HIV-infected patients with intra-anal LSIL or HSIL: multifocal lesions were seen in 76% and anal HSIL in 74%¹⁶. In this study, 1 g of 5FU 5% was inserted using an applicator twice weekly at night for 16 weeks. Complete responses were seen in 12 of 34 patients with anal HSIL and partial responses with a decrease in HSIL to LSIL were seen in an additional 8 subjects. Thirty-nine participants (85%) experienced side effects, but only 2 participants discontinued treatment early. Snyder and colleagues reviewed 11 patients using 0.25 g of 5FU placed intra-anally at bedtime for a median treatment time of 20 weeks¹⁷. One patient discontinued therapy due to side effects and 73% of patients experienced anal pain or irritation. Five of nine patients with HSIL at baseline had improvement in their disease, although 8 of 9 had HSIL on post treatment biopsies.

Jay et al. described the results of a trial from the UCSF Anal Neoplasia Clinic using intra-anal 5FU 5% twice daily for 5 days, followed by a 9-day rest period¹⁸. The cycle was repeated 4 times and patients re-evaluated. Twenty patients with extensive anal HSIL involving more than 75% of the circumference were evaluable. Complete histologic regression was seen in 3 patients, a significant decrease in the volume of disease allowing ablation was observed in 16 patients, and 1 had no response. The side effects included pain, ulceration, bleeding, and exacerbation of herpes simplex. However, only 2 of 27 discontinued treatment because of side effects and 4 were considered non-adherent and not evaluable because they completed less than 2 cycles.

Richel et al. reported on 148 HIV-infected men who have sex with men with squamous intraepithelial lesions (57% with HSIL) randomized to 4-month treatments with 2% 5FU, 5% imiquimod, or monthly electrocautery¹⁹. The complete response rate (i.e. no SIL noted on post-treatment biopsy) was 17%, 24%, and 39%, respectively in the intention to treat group with severe side effects reported as 27%, 43%, and 18%, respectively. Recurrence rates were 58%, 71%, and 68% at 72 weeks post-treatment. In the group with HSIL, the complete or partial response rate was 43%, 46%, and 68% respectively. This is the only report comparing 5FU to imiquimod in a randomized study.

IMIQUIMOD

Imiquimod has been used for treatment of external genital warts since 1997. It is an imidazoquinoline amine, which is a topical synthetic compound that upregulates the adaptive and innate immune systems to exert antiviral activity and to treat dysplastic tissue by inducing apoptosis through the intrinsic pathway²⁰. The indirect mechanism is binding cell surface receptors resulting in secretion of a variety of inflammatory mediators including interferon alpha, TNF-alpha, IL-12, IL-1, 6, 8, and 10. These cytokines then activate the cell-mediated immune response and in turn the release of interferon-gamma, responsible for activating cytotoxic T-cells and natural killer cells in the local environment²¹. Imiquimod has no direct antiviral activity or direct effect on T-cells but is a strong inducer of Th-1 type

cytokines resulting in recruitment of dense CD4+ infiltrates, which is an important mechanism for HPV clearance and one that is reduced in HIV-infected populations.

Off-label use of imiquimod is common in both skin and mucosal disease^{22, 23} with extensive case reports noted in the medical literature. Imiquimod has been reported for treatment of infectious diseases including molluscum contagiosum, genital herpes and cutaneous leishmaniasis^{24–26} Finally, imiquimod has been used for treatment of vulvar, penile and anal squamous intraepithelial lesions^{27–31}.

Imiquimod has demonstrated efficacy for the treatment of anogenital condyloma in a series of randomized clinical trials³². Response rates to imiquimod for genital condyloma are better in HIV-negative patients compared to HIV-positive patients, with response rates of 62% and 31% respectively³². The role of imiquimod in clearing anal HPV infection in patients with anogenital condyloma was investigated in a single arm study involving 239 HIV-infected and -uninfected men and women. At baseline, 95% had low risk HPV, 60% had high risk HPV, and 56% had both. Condyloma were treated with imiquimod 5% cream for external warts and suppositories for intra-anal disease, three times a week for 26 weeks. At 12 weeks, 30% of subjects with high-risk HPV had cleared their infection as did 66% of subjects with low-risk HPV³³.

There are limited reports describing the efficacy of imiquimod 5% for treatment of anal HSIL³⁴. Imiquimod is also available in 2.5% and 3.75% formulation. These formulations have an FDA indication for treatment of actinic keratosis in adults and for treatment of external genital warts (EGW)³⁵. In one study, 14 of 19 (74%) HIV-positive MSM with intra-anal and/or perianal LSIL or HSIL had complete regression of SIL after treatment with imiquimod 5%³³. Among 13 patients with HSIL at baseline, 9 (69%) cleared HSIL at the end of treatment. A decrease in the number of HPV types and HPV viral load was also seen following treatment. Fox et al conducted a randomized, double-blind placebo controlled study of imiquimod 5% for anal HSIL enrolling 53 patients³⁶. Among 28 patients in the imiquimod arm, 4 had complete HSIL resolution and 8 downgraded from HSIL to LSIL. Only 1 subject of 25 in the placebo arm experienced complete resolution of HSIL.

CIDOFOVIR

Cidofovir is a cytidine nucleotide analogue with activity against a broad spectrum of viruses including herpes viruses, adenoviruses, and HPV³⁷. It is FDA approved for cytomegalovirus retinitis. Cidofovir causes selective inhibition of HPV-infected cell proliferation³⁸ and increases the levels of the tumor suppressor protein p53³⁹. Cidofovir produces a selective cytotoxic effect against HPV-infected cells because they concentrate dephosphorylated cidofovir while normal cells concentrate a different form of cidofovir⁴⁰. Induction of apoptosis causes cell death after successful cidofovir treatment³⁸.

Cidofovir has been studied for the treatment of genital and anal condyloma, and anal HSIL. As with the other topical patient-applied treatments the dosing regimens vary widely^{41–46}. Cidofovir 1% in cream or gel was compared to electrocoagulation for the treatment of condyloma in a small study of 20 subjects. The complete or partial response rate was 92%

with the use of the 1% gel versus 55% with ablation⁴¹. A large randomized study enrolling HIV-infected patients with genital condyloma compared electrocautery alone, 1% cidofovir gel alone 5 days a week for up to 6 weeks, and electrocautery followed by cidofovir 5 days a week for 2 weeks initiated 4 weeks after electrocautery. Complete response rates for the three arms were 93%, 76% and 100%, respectively. Recurrence rates were 74%, 35% and 27%, respectively and clearly showed the benefit to cidofovir treatment⁴⁴.

There was a single arm clinical trial enrolling 33 HIV-infected adults with perianal HSIL; 8 female participants had vulvar HSIL as well⁴⁷. All participants self-applied 1% cidofovir gel to the lesions once daily, leaving it in place for 6-8 hours before washing it off. Treatment continued for 5 days followed by 9 days off. This two-week cycle was repeated 6 times. Twenty-six participants (79%) completed the treatment course. A complete response was observed in 5 (15%), partial regression in the extent of HSIL was observed in 12 (36%), 7 (21%) had stable disease, and 2 had progression (1 developed a superficially invasive cancer and 1 developed a new HSIL during 16 weeks of followup). Seventeen patients were enrolled in a pilot clinical trial of 1% cidofovir 2 grams applied intra anally 3 times a week for 4 weeks⁴⁸; 63% cleared HSIL when assessed at 12 weeks. The main limitation of cidofovir is that there are no commercial preparations available; the cream or gel must be prepared for individual patients by a compound pharmacist and it might not be covered by standard insurance.

TCA

Topical trichloroacetic acid (TCA) is recommended by the Center for Disease Control as a first-line therapy for perianal condyloma⁴⁹. TCA is caustic and corrodes the skin and mucous membranes. It treats HSIL by denaturing and precipitating proteins resulting in tissue destruction⁵⁰. TCA is provider-applied in the office setting and has the advantage over other topical treatments of not requiring patient adherence other than repeated office visits for treatments. TCA has not been reported to have any systemic side effects and is well tolerated by patients (see Chart 2). TCA is the only topical treatment that is safe to use in pregnancy⁴⁹.

TCA treatment requires HRA to identify and locate HSIL. Wooden-tipped cotton applicators are used to apply TCA. The cotton end is dipped in the TCA to partially saturate the cotton. The liquid should be absorbed only halfway through the cotton to avoid oversaturation and dripping of TCA. Some providers dip the wooden end of the cotton applicator into the TCA to allow more precise application of the TCA. These applicators are then inserted through the anoscope and guided to the lesions. TCA is applied by touching the applicator to the lesion repeatedly until the area becomes opaque, dense, and snow-white in appearance. Allowing time for drying prevents the acid from spreading to unaffected areas. Four or five applications are typically needed to completely treat the lesion. Treatment concentrations of TCA are not standardized, but the studies reviewed use concentrations of 80-85%^{51, 52}. Only very small amounts of TCA should be in the procedural field and it should be properly labeled to avoid being mistaken for acetic acid or other liquids.

Multiple treatment visits are typically required, usually spaced 3-4 weeks apart. A retrospective review of HIV-infected men diagnosed with anal SIL who were treated with TCA in up to 4 separate treatment visits found that 61% of patients cleared to LSIL or no lesion⁵¹. Greater clearance was seen among men who were younger in age (<49 years) or had 2 or fewer lesions requiring treatment. Another larger retrospective review described men diagnosed with HSIL over a three-year period⁵². This study evaluated outcomes of 98 HSIL lesions 3-6 months after TCA treatment. Patients with areas of disease that extended beyond 25% of the anal circumference for an individual lesion or beyond 50% for all lesions were not treated with TCA because of theoretical concern for scarring. Seventy-nine percent of the treated lesions improved to LSIL or resolved to normal epithelium or during the time of follow up. They also found that a single TCA treatment course improved or resolved 49% of the lesions, with 27.6% requiring two treatment courses for similar outcomes.

TCA may not be appropriate for treating extensive or bulky disease, but does, however, offers a treatment option for HRA providers not yet able to offer other ablative therapies. TCA is a safe and low cost treatment with fewer adverse events compared to other treatments for HSIL.

Adverse event management

Adverse events occur commonly during treatment with patient-applied topical therapy. The most common adverse events are pain, irritation, erythema, and ulceration at the site of application. Patients should be advised to avoid exposure to areas without HPV lesions such as perineum, lower vulva or scrotum. Imiquimod may also lead to systemic side effects such as influenza-like symptoms. Although side effects occur in the majority of patients, permanent discontinuation of the treatment course is uncommon. Side effects after provider applied trichloroacetic acid appear to be minimal.

Side effects troublesome to the patient or that interfere with normal activities may be managed using topical analgesics and/or dose modification. There are FDA-approved cream formulations of lidocaine, prilocaine and tetracaine available for intra-anal use. Patients can apply the cream prior to bowel movements and at other times for symptomatic relief. Patients experiencing burning sensation may experience some benefit from warm baths⁵³. These strategies are generally successful for milder symptoms. For patients experiencing more significant side effects, dose interruption should be considered until the side effects have lessened in intensity. Treatment can be restarted at a reduced dose. (Table 2) If the patient tolerates the reduced dose, dose escalation to full treatment dose can be considered after a few weeks of the reduced schedule.

Dose application and adherence support

Patient-applied topical therapy needs to be applied to the site of disease for optimal efficacy. For intra-anal disease, this means applying the cream from the squamocolumnar junction distally to the anal verge. Most patients are able to do this by self-applying the cream using a gloved finger inserted into the anus. Some providers recommend splitting the dose and applying with the left and right hands to ensure complete coverage. If possible, patients should be observed applying a dose in the office. This will identify any challenges for self-

administration and allow for additional education. There are no specific anal applicators designed for this purpose. If using an applicator or syringe, care must be taken to avoid inserting the cream beyond the anus into the rectum. This will lead to loss of efficacy and may lead to additional side effects such as proctitis.

Patients should be counseled on the importance of sustained adherence and the need to communicate occurrence of side effects that are beyond mild. It may be reassuring for patients to know that side effects may indicate treatment efficacy. Many of the dose schedules are intermittent; calendars or electronic reminders should be offered to remind patients of the dosing schedule. An interim visit within 4 weeks of initiating treatment is advisable to identify unexpected challenges in administration, to survey for side effects and to support adherence.

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Summary

There are viable topical treatment options for anal HSIL, and they are appealing for patients with extensive HSIL or patients with contraindications to ablative therapies. Provider-applied trichloroacetic acid appears to have minimal side effects and is a reasonable treatment option for patients with focal HSIL opting for a non-surgical approach. Patient-applied imiquimod and 5FU appear to have efficacy against anal HSIL and are available by prescription, but robust data from randomized clinical trials are lacking. Even if complete resolution of HSIL is not achieved, a reduction in the amount of disease may allow for less extensive ablative treatment of residual disease. These treatments cause frequent side effects and prescription of topical analgesics and/or dose reductions are often needed. However, the vast majority of patients are able to complete treatment courses. Further studies are needed to further define the efficacy of these treatments and their optimal role in the management of anal HSIL.

Table 1

Clinical trials and case series reporting topical treatment of anal HSIL

Treatment	Dosing Regimen	N	Clearance to Normal or LSIL pathology	Adverse Events	Reference
TCA	1-4 in-office applications	72 HIV+ (92 lesions)	79% (50% after one tx) of lesions	Not specifically reported Rates reported to be similar to those experienced with HRA with biopsies	52
	1-4 in-office applications	54 (35 HIV+)	61%	5% local discomfort or pain No serious adverse events	51
Imiquimod 5%	5 consecutive nights per week for 32 weeks (half packet per dose formulated in suppository)	44 HIV+	45% at 16 weeks 66% at 32 weeks	96% pain during defecation 57% anal burning 11% fatigue	54
	3 nights a week for 16 weeks (half packet per dose)	28	43% at 16 weeks	one patient discontinued due to side effects	36
	3 nights a week for 16 weeks (half packet per dose)	24 HIV+	46%	90%	19
5-FU 2%	1g twice weekly for 16 weeks	28 HIV+	43%	92%	19
	1g twice weekly for 16 weeks	34 HIV+	59%	85% (only 2 d/c'd treatment)	16
5-FU 5%	Approximate pea-sized amount every evening	9 HIV+	11% (additional 44% had reduced HSIL volume)	73% (most perianal irritation) 1 severe reaction after 4 days	17
Cidofovir 1%	2g 3 times a week for 4 weeks	17 HIV+	62% (at 12 weeks)	81% (local only) No discontinuations	48
	"Thin layer" daily for 5 days, followed by 9 days off; repeat for 6 cycles	33 HIV+	15% (additional 36% had reduced HSIL volume)	97% (most local discomfort) 75% pain burning and irritation 39% ulceration	47

TABLE 2

Dosing of patient-applied topical therapy for anal HSIL

	Topical 5-fluorouracil 5%	Imiquimod 5%	Cidofovir 1%
Standard dose	0.5 mL (0.5 gm) applied intra-anally twice daily for 5 days followed by 9 days off	0.5 to 1 packet applied intra-anally 3 times a week at night	1 mL (1gm) applied intra anally daily at night for 5 days followed by 9 days off
Reduced dose	0.5 mL (0.5 gm) applied intra-anally twice daily for 3 days followed by 11 days off	0.5 to 1 packet applied intra anally 2 times a week at night	1mL (1gm) applied intra anally daily at night for 3 days followed by 11 days off
Minimal dose	0.5 mL (0.5 gm) applied intra-anally daily for 3 days followed by 11 days off	0.5 to 1 packet applied intra anally once a week	0.5 mL (0.5 gm) applied intra anally daily at night for 3 days followed by 11 days off

Note: additional cream may be needed to treat perianal disease.