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Review

Update on the treatment of genital warts

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Abstract

This review summarizes new treatments from the last seven years employed for the treatment of genital warts caused by human papillomavirus (HPV). **Imquimod 3.75%** is a new agent with fewer side effects and perhaps a better dosing schedule than imquimod 5%, but is not more effective. **Sinecatechins/Polyphenon E 15%,** a novel extract from green tea can be effective against genital warts but requires three times a day dosing and is not more effective than existing treatments; the treatment course is 12-16 weeks. **Photodynamic therapy** combined with other destructive modalities might increase the cure rate for genital warts. The **quadrivalent vaccine** against HPV 6, 11, 16, 18 is decreasing the incidence of warts in the western world but the evidence does not support vaccination as a treatment for those already infected by HPV. Hyperthermia and immunomodulators might be positive additions to the armamentarium of clinicians. In sum, there are new tools that physicians can use but none is really a great advance over what was available a decade ago.

Introduction

This article is an update on a prior article that was published in the DOJ in 2006 on the treatment of genital warts. Since that time new topical agents have come on the market that the FDA and other similar regulatory agencies have approved. One is sinecatechin and the other is imquimod 3.75%. Moreover, there are several new agents that are not approved, but show promise in this regard. Perhaps the most important development for public health as it concerns genital HPV is the development of two vaccines. Quadrivalent human papilloma virus (HPV) [types 6, 11, 16, 18] and recombinant vaccine (Gardasil®; Silgard®) are composed of virus-like particles (VLPs) formed by self-assembly of recombinant L1 capsid protein from each of the HPV types 6, 11, 16, and 18. The bivalent vaccine is expected to be slightly more effective at preventing CIN2 and -3 and SCC in the longer term. The quadrivalent protects against HPV 6, 11, 16,18 and the bivalent vaccine protects against HPV 16 and 18. In addition photodynamic therapy has shown promise in the treatment of genital warts and this will be reviewed in brief.

New Treatments

Imiquimod 3.75% cream

In 2010, the FDA approved Imiquimod 3.75% cream for the treatment of genital warts [1, 2, 3]. It is avaiable in a 7.5g pump that dispenses 0.235 g of cream per full actuation of the pump after priming. Two Phase III, double-blind, placebo-controlled studies have shown imiquimod 3.75% to be significantly more effective than placebo, achieving a 33-percent clearance rate in a protocol evaluation and a 28-percent clearance rate in an intention-to-treat study. Furthermore, recurrence rates were relatively low, with up to 85 percent of subjects achieving complete clearance at a 12-week follow-up evaluation. Imquimod 3.75% should be applied to warts for 8 hours and is dosed daily for two weeks of treatment with repeat two week treatments after a two week rest period. Imquimod 3.75% is indicated for the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older. Primary cure rates for the 3.75% imiquimod are not as high as the 5% imquimod. However, the newer product is thought to have some advantages over the 5% imquimod with respect to patient compliance. Significantly, the 3.75% imquimod is available in a dose metered pump and the duration of treatment for the 3.75% imiquimod is significantly less prolonged, with daily application required for a maximum of eight weeks of treatment [4] vs 16 weeks of continuous every other day treatment for the 5% imquimod [5]. Additionally, the 3.75% cream has fewer side effects than the 5% imquimod. The main complaints include itching, burning, or pain at the site of application [6]. Unlike the 5% cream, no systemic symptoms have yet been associated with

3.75% imquimod. However, 3.75% imquimod is a patented product and is thus more expensive than an equivalent amount of the 5% sachets.

Sinecatechins/Polyphenon E

Sinecatechins (Veregen® or Polyphenon E, Kunecatechin) is an extract from green tea (*Camellia sinensis*) contained in a 15% ointment and was approved by the FDA in 2008 for the treatment of genital warts [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. One article suggests that the 10% sinecatechins ointment is also effective against genital warts [21]. One study has suggested that sinecatechins are a more cost effective treatment than imquimod for the treatment of genital warts [22]. Based on the efficacy of sinecatechins 15% ointment, the 2010 CDC STD Treatment Guidelines for HPV and genital warts were amended to include sinecatechins 15% as a treatment for genital warts.[23]

Sinecatechins contains catechins, in particular epigallocatechin gallate, that has shown activity as an agent with potent activity againt cancerous and virally infected cells. Based on international trial data of 397 patients, the FDA approved sinecatechins ointment 15% for the topical treatment of external genital and perianal warts (condylomata acuminata) in immunocompetent patients aged ≥18 years. It is used three times a week for up to 16 weeks. In the subset of 30 United States participants, 5 achieved total clearance at 16 weeks (23.8%), whereas none of the placebo group experienced total clearance. Whereas less than 5% of study patients had to drop out owing to side effects, about 67% experienced some types of side effect, the most common of which were: erythema, erosion, edema, itching, burning, pain, induration, and vesicular eruptions. In sum, sinecatechins is the first botanical treatment for condyloma and brings about what is hoped to be a new age of botanical treatments that will enhance health and combat disease. The mode of action of sinecatechins ointment 15% in the clearance of genital and perianal warts is unknown. In vitro, sinecatechins had anti-oxidative activity; the clinical significance of this finding is unknown

The efficacy of sinecatechins in the treatment of external genital and perianal warts was assessed in 2 randomized, double-blind, vehicle-controlled studies designed to investigate the safety and efficacy of sinecatechins ointment (10 and 15% concentrations) in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The side effects were mostly mild. This study was carried out in the United States and in other cities worldwide. There were detailed exclusion criteria and inclusion criteria used in these clinical trials. The clinical subjects in this study applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment). Over both studies the median baseline wart area was 51 mm^2 (range 12 to 585 mm^2) and the median baseline number of warts was 6 (range 2 to 30). The primary efficacy outcome measure was the response rate, defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16.

In data contained in the new drug application (NDA) submitted to the FDA, patients (N=397) applied the 15 % ointment 3 times per day for up to 16 weeks or until all warts were cleared. Among patients from all countries including the United States, 213 (53.6%) patients treated with sinecatechins experienced complete clearance versus 73 (35.3%) patients treated with vehicle. Among patients from the United States (n=30), 5 (23.8%) sinecatechins-treated patients experienced complete clearance versus 0 patients treated with vehicle. Men treated with sinecatechins (n=205) experienced lower clearance rates than women (n=192; 47.3% vs 60.4%, respectively), a trend also observed among patients treated with vehicle. The median time to complete wart clearance for patients treated with sinecatechins was 16 weeks in the first trial and 10 weeks in the second trial.

In a subset of data, the European trial (carried out in a total of 48 hospitals in 7 European countries) achieved all objectives of the trial. Approximately 53 % of the patient treated with the 15 % sinecatechins ointment showed complete clearance of all external genital warts (clear statistical significance $p = 0.01$ compared to placebo). Approximately 51% of the patient treated with the 10 % sinecatechins ointment showed complete clearance of all external genital warts (clear statistical significance $p = 0.03$ compared to placebo). Approximately 37% of the patient treated with placebo showed complete clearance of all external genital warts (clear statistical significance $p = 0.01$ compared to placebo). The secondary objectives of the trial were also achieved: complete recovery from warts that already existed at the beginning of the treatment (baseline warts) of 55 % of the patients with 15 % ointment, of 53 % of the patients with 10 % ointment, and of 36 % of the patients treated with placebo (clear statistical significance compared to placebo: $p = 0.01$ for 15 % ointment, $p = 0.03$ for 10 % ointment). In about 78 % of all patients treated with sinecatechins 15 % ointment, most or all of the genital warts disappeared. Recurrence of genital warts during the twelve weeks of follow-up occurred in a very small number of patients (less than 5 %).

The results of these studies have been presented at several scientific conferences: the 13th Congress of the European Academy of Dermatology and Venereology (November 2004, Florence, Italy), the International Herpes Papilloma Virus Symposium (May 2005, Vancouver, B.C., Canada), the Society of Investigative Dermatology Meeting (May 2005, St. Louis, MO), and the HPV and Skin Cancer Conference (September/October 2005, Berlin). The most recent conference was in October 2005 at the 14th Congress of the European Academy of Dermatology and Venereology in London.

Side effects

In clinical trials in the United States, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). Sinecatechins have been shown to undermine the integrity of the latex contained in condoms and vaginal diaphragms. Sinecatechins should not be put on open wounds. The eyes, vagina, and anus can be irritated by sinecatechins and thus contact of mucosal surfaces should be avoided. Sinecatechins commonly cause local skin reactions. In clinical trials, persons using sinecatechins manifested phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes, vulvitis, skin ulceration, erosions in the urethral meatus, and superinfection of warts and ulcers. In clinical trials, in a handful of cases clinical subjects noted urethritis, peri-anal infection, pigmentation changes, xerosis, eczema, hyperesthesia, necrosis, papules, discoloration, cervical dysplasia, pelvic pain, cutaneous facial rash, and staphylococcemia. In clinical trials, clinical subjects noted, most commonly with kunecatechin use: erythema, erosion, edema, itching, burning, pain, induration, and vesicular eruptions.

A total of 266/397 (67%) of subjects in the sinecatechins 15% ointment group had either a moderate or a severe reaction that was considered probably related; of these 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts, and 48% (11/23) of subjects with perianal warts only. Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with sinecatechins and in 1% (1/99) in vehicle. Less common adverse events included: cervical dysplasia, pelvic pain, cutaneous facial rash, and staphylococcemia. In a dermal sensitization study of sinecatechins ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

Sinecatechins are indicated for use 3 times per day to all external genital and perianal warts. Treatment should be continued until all warts are cleared but should not be continued for greater than 16 weeks. Sinecatechins is not a cure for external genital and perianal warts and new warts may develop during or after a course of treatment. The safety of treating external genital and perianal warts for greater than 16 weeks or for multiple treatment courses has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The Maximum Recommended Human Dose (MRHD) of 15% sinecatechins ointment was set at three times daily topical administration of 250 mg (750 mg total) containing 112.5 mg sinecatechins for the animal multiple of human exposure calculations presented in this labeling. Dose multiples were calculated based on the human equivalent dose (HED).

In an oral (gavage) carcinogenicity study, sinecatechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD). Treatment with sinecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Sinecatechins ointment 15% has not been evaluated in a dermal carcinogenicity study. Sinecatechins gave negative results in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but gave positive results in the mouse lymphoma mutation assay. Daily vaginal administration of sinecatechins ointment 15% to rats from day 4 before mating and throughout mating until day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

Sinecatechins is pregnancy category: C. Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of sinecatechins during the period of organogenesis (gestational days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of sinecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study. A combined fertility / embryo-fetal development study using daily vaginal administration of sinecatechins ointment 15% to rats from day 4 before mating and throughout mating until day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of sinecatechins ointment 15% at doses of 0.05, 0.10, and 0.15 mL/rat/day from day 6 of gestation through parturition and lactation. The high and intermediate dose

levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F0 dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction, and fertility at any dose tested. There are no adequate and well-controlled studies in pregnant women. Sinecatechins ointment 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Special Patient populations

It is not known whether topically applied sinecatechins is excreted in breast milk and thus its use should be avoided in nursing mothers. Safety and efficacy in pediatric patients have not been established and thus its use should be avoided in children. Seven patients (1.4%), older than 65 years of age, were treated with sinecatechins in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

Dosage,AdministrationSupply,Storage

Sinecatechins ointment 15% is to be applied three times per day to all external genital and perianal warts. It is recommended to wash the hands before and after application of sinecatechins. About a 0.5 cm strand of the sinecatechins ointment 15% should be applied to each wart using the finger(s). It should be dabbed on to ensure complete coverage; a thin layer of the ointment should remain on the warts. It is not necessary to wash off the ointment from the treated area prior to the next application. The package insert of sinecatechins has included a list of specific information to be given to patients regarding sinecatechins and precautions for its use.

Treatment with sinecatechins should be continued until complete clearance of all warts, but no longer than 16 weeks. Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable. Sinecatechins ointment 15% is a brown ointment and is supplied in aluminum tubes containing 15 grams of ointment per tube. Prior to dispensing to the patient, store refrigerated. After dispensing, it can be stored either refrigerated or up to 25°C (77°F). Sinecatechins ointment should not be frozen.

Quadrivalent vaccine for the treatment of genital warts

In 2006, the FDA approved the use of the first HPV vaccine, (Gardasil® Merck & Co.) [6]. The recombinant, quadrivalent vaccine was intended for the prophylactic treatment of girls and young women 9 though 26 years of age for the prevention of the following pathologies caused by HPV types 16 and 18: cervical, vulvar, and vaginal cancer and condyloma acuminata. In addition, quadrivalent vaccine is indicated for the prevention of precancerous or dysplastic lesions caused by HPV 6, 11, 16, and 18. The quadrivalent vaccine triggers the formation of human antibodies to the 6, 11, 16, 18 HPV subtypes, which are directly responsible for approximately 90 percent of genital warts and 70 percent of cervical cancers. The quadrivalent vaccine injections are administered in three separate doses and appear to be 99-percent effective in preventing genital wart formation in patients naïve to HPV infection. In the fall of 2009, the FDA licensed a recombinant, bivalent HPV vaccine (Cervarix® GlaxoSmithKline) for use in females ages 10 though 25 years. It seems more effective in preventing cancer than the quadrivalent vaccine. Thus far, there is only one randomized, observer-blinded, head-to-head study comparing these two vaccines in a single, well-defined population of more than 1,100 healthy women ages 18 to 45 years. Results of this study showed that HPV-16 and HPV-18 neutralizing antibodies induced by HPV2 were higher than those induced by HPV4 across all age strata (p<0.0001). The observed differences in immune response induced by the two vaccines could relate to differences in formulation, particularly with regard to adjuvant factors that enhance the immune response to vaccine antigens. Although the clinical importance of this difference in immune response is unknown, they may represent determinants of duration of protection against HPV-16 and 18 [24].

Whereas quadrivalent vaccine can prevent the development of warts in those who are not infected, it seems to have little effect on those who are infected. In 2007, a large randomized trial in women with existing high-risk HPV infection showed that quadrivalent HPV vaccination does not accelerate clearance of the virus and therefore should not be used to treat active infections [25]. This observation was confirmed again in 2011 [26]. In one patient first treated with imquimod without success, warts cleared with administration of the quadrivalent HPV vaccine, but the significance of these finding are unclear [27]. In a small study of 6 patients with varying types of HPV who were given vaccination and treated with electrocautery [27], all patients experienced recurrences (mean number of recurrences: 4.8; range, 1-11) of at least 1 condyloma after HPV vaccination. HPV typing of the condyloma performed at first presentation and at the time of recurrence showed that the respective HPV types had probably persisted in the patients [28].

Photodynamic Therapy

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) is an emerging technique for the treatment of genital human papillomavirus (HPV) [29-45]. PDT was effective in a series of 4 treatments for the treatment of gential warts in pregnant women [30]. Chen showed that topical application of ALA-PDT is a simpler, more effective, and safer therapy with a lower recurrence for treatment of condylomata compared with conventional CO^2 laser therapy [32]. Szeimies showed that adjuvant ALA-PDT of condyloma accuminata after CO^2 laser ablation was well tolerated, but no significant difference with regard to recurrence rate was observed as compared to CO^2 laser vaporization alone [33]. Herzinger performed a small open study using topical 5-ALA and red light (630 nm) in nine men with genital condylomata and a history of at least one previous unsuccessful conventional treatment. Complete cure was achieved in three patients, one of whom experienced a relapse after 3 weeks. Three patients showed partial responses and three showed no response [34]. Liang [35] used photodynamic therapy (PDT) with topical application of 20% wt/vol aminolevulinic acid hydrochloride (ALA) in 91 patients. The response rate was close to 100% and there were fewer side effects than with the CO^2 laser. The side-effects in patients treated with ALA-PDT mainly included mild burning and/or stinging restricted to the illuminated area. Wang [36] studied 56 patients who had cervical lesions and were treated with PDT by applying ALA gel (10%) to the surface of the cervix for 4 h followed by irradiation with a 635 nm laser at 100 J cm^2. PDT was repeated at 2-week intervals if the lesion and HPV infection remained. Patients were followed up for 6-24 months. Genotyping analysis revealed four HPV subtypes (HPV6, 11, 16 and 18). The overall complete remission rate of 1-4 sessions of treatments was 98.2% and the corresponding HPV clearance rate was 83.9%. Ten cases showed complete removal of cervical lesions and HPV infection after a single treatment. Recurrence rate was 3.6%. Lu [41] studied 40 patients with anogential warts; after three PDT sessions following surgical curettage, all 40 patients were cured and there was no recurrence at 1 month off treatment. At 3 months off treatment, six cases relapsed, corresponding to a recurrent rate of 15%. The satisfaction rate of patients was 100% at 1 month and 95% at 3 months after treatment. Li studied 35 men and found that liquid nitrogen freezing combined with 5-aminolaevulinic acid-photodynamic therapy for condyloma acuminatum in men was effective [45]. In sum, whereas PDT is not a cure all it might be a useful adjuvant to other destructive modalities for the treatment of genital warts

Other experimental treatments for genital warts: single case reports

Huo[46] treated three diabetic patients with extensive genital warts by local hyperthermia at 44 °C for 30 min a day for 3 consecutive days plus 2 additional days 1 week later, then once a week until there were signs of clinical clearance. Immunohistochemical profile was described on serial biopsies from a patient with confluent plaques. The warty lesions in the patients resolved in 6, 4, and 9 weeks, respectively.

Domínguez Gómez[47] studied glycyrrhizinic Acid (glizigen) and an immunostimulant, viusid, in 100 patients. All were diagnosed clinically with anogenital warts. The patients were assigned to two groups of 50 individuals. Those from one group where treated with glizigen and viusid and those from the other group with 25% podophyllin in alcohol; the results from each were then compared. The combined glizigen-viusid treatment was seen to have an 87.5% efficacy rate, which was slightly more than that of the treatment with podophyllin and there were only rare adverse reactions reported during the treatment.

Jardine[48] studied immunotherapy with HPV6 L1 virus like particles (VLPs) without adjuvant (VLP immunotherapy) and found that this reduces recurrence of genital warts following destructive therapy. A randomized placebo-controlled, blinded study of treatment of recurrent genital warts amenable to destructive therapy was conducted independently in Australia and China. Patients received conventional destructive therapy of all evident warts together with intramuscular administration of 1 μg, 5 μg, or 25 μg of VLP immunotherapy or of placebo immunotherapy (0.9% NaCl) at week 0 and week 4. Primary outcome, assessed at week 8, was recurrence of visible warts. Of 33 protocol compliant Brisbane recipients with placebo immunotherapy, 11 were disease free at two months and a further 9 demonstrated reduction of greater than 50% in total wart area. Wart area reduction following destructive treatment correlated with prior duration of disease. Among 102 protocol compliant Brisbane recipients of VLP immunotherapy, disease reduction was significantly greater than among the placebo immunotherapy (50% ± s.e.m. 7%) recipients for subjects receiving 5 μg or 25 μg of VLP immunotherapy/dose (71% ± s.e.m. 7%), but not for those receiving 1 μg VLP immunotherapy/dose (42% ± 7%). Of 52 protocol compliant placebo immunotherapy recipients in Wenzhou, 37 were disease free at two months and a further 8 had greater than 50% disease reduction. Prior disease duration was much shorter in the Wenzhou study subjects (8.1 ± 1.1 mo) than in Brisbane subjects (53.7 ± 5.5 mo). No significant reduction in mean wart area was observed for the 168 Wenzhou protocol compliant subjects who also received VLP immunotherapy.

Conclusion

Genital warts continue to present significant morbidity in the United States. They result in sexual dysfunction and depression among males [49]. At entry, 29 of 200 (14.5%) male armed service members were positive for HPV serotypes 6, 11, 16, or 18. Of 199 initially seronegative for at least one of the four HPV serotypes, 68 (34.2%) seroconverted to one or more serotypes at ten years. More than one-third of these were seropositive for oncogenic HPV serotypes [50]. There is hope in the future that use of the quadrivalent HPV vaccination will decrease the burden of genital warts and cervical cancer. Results of those vaccinated in Denmark [51] and Sweden [52] show that the incidence and prevalence of warts is falling in those who were inoculated. In

conclusion, new treatments are being added to the armamentarium of physicians. It is not clear if they are better than those in use in the past, but the new modalities do give more tools to the clinician. In addition, with the use of vaccines against genital warts the morbidity of warts at least in the western world will fall in decades to come. Although definitive treatment has not emerged in the last 7 years since my last review was written, progress in the fields of genital HPV treatment and prevention have moved forward.

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