Overview of HPV-related Dermatoses and Applications of Sinecatechins Ointment

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Abstract The incidence of *Condyloma acuminata* and other HPV-related dermatoses is increasing, with as many as one million new cases of infections diagnosed yearly. Therapeutic options that were once limited to in-office procedures or topical podophyllin toxins are now directed toward modifying the immune responses against the viral burden and minimizing recurrence potential. For years, compliance with follow-up and topical management has been limited due to issues with convenience, toxicities, and costs. There are now several pharmacological agents in the dermatology marketplace that can be incorporated into treatment regimens, either as monotherapy or in combination with in-office destruction modalities. One of the newer agents, Sinecatechins 15 % ointment (Veregen®), promotes localized antioxidative effects in conjunction with other proinflammatory actions. As the elucidations of the immune mechanisms that create viral diseases as well as other dermatoses continues to expand, so will the potential applications of this class of therapies. Several studies have supported its use in the treatment of external genital warts as well as other diseases. This article focuses on the pathogenesis and epidemiology of external genital warts and other manifestations of HPV, as well as on the history, mechanisms of action, and therapeutic applications of Sinecatechins 15 % ointment.

Keywords Sinecatechins · Antioxidative · External genital warts · Compliance · Cervical cancer

Introduction

The diagnosis of external genital warts (EGW) is increasing and is a disease that is not limited to any specialty. Family physicians, gynecologists, dermatologists, and practitioners in sexually transmitted disease (STD) clinics are among the many clinicians who are diagnosing and treating EGW [1]. Almost 12 years ago in the year 2000, a study reported nearly 19 million new cases of STDs in the United States; of that number, 6.2 million new patients aged 15–44 years were diagnosed with “HPV infections,” and the most common manifestation was *Condyloma acuminata* independent of body location [2]. Of these newly diagnosed patients, almost half of all new STDs and nearly 74 % of new cases of warts occurred in 15- to 24-year-olds.

Since 2000, several other reports have documented the rising incidence of EGW, including a retrospective analysis in 2004 that revealed more than 20 million Americans were newly diagnosed, including 9.2 million between the ages of 15 and 24 years [3•]. In that year, it was predicted that anywhere from half a million to a million new cases of EGW are diagnosed annually [4•].

More importantly, the economic burden caused by HPV infections on healthcare overall, ranging from evaluations and treatments for warts, vaccinations, screening evaluations, and treatment for cervical cancer, was estimated at more than four billion dollars [5]. This amount would be even higher considering that external genital wart infections are not reported to state health departments and documenting cases would comprise a significant task for health departments [3•]. However, unlike other STDs, there are limited data on prevalence and incidence of HPV infection, because there is no routine screening for HPV, especially in males where there is no screening tool equivalent to the pelvic exam and Pap smear in females. In addition, it is not clear whether a newly diagnosed infection is recently

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acquired or long-standing, of a virulent or nonvirulent subtype, or a recurrence from a previous infection in another body location [3••].

Age-related variations also are influential on the increases in prevalence, and current data suggest that although the teenage and college-age populations show higher infection rates, certain factors that increase risk of infection, such as higher number of sexual partners, higher patient numbers using nonbarrier forms of contraception (e.g., IUD, OCPs), and shorter time interval between meeting a new partner and sexual intercourse [6•], might account for an increase in prevalence in ages 30–44 years. In the face of a higher divorce rate and more adults dating new potential partners, these numbers may continue to rise.

Gender Differences and Variations

The concern also is for the number of individuals who are infected with multiple strains of the virus. It was reported that almost 75 % of patients are infected with high-risk HPV types [3••] and nearly 30 % have warts with multiple HPV types [7••, 8•]. There are several parallels in the gender distribution of EGW and the viral strains involved, which at the time of publication was important given that the vaccine series was only approved for females [9].

In 2006, a review of 23 published studies from 1994 to 2004 was published that summarized the epidemiology of HPV among women in the United States [10]. The research showed that the prevalence of EGW in females varies from 14 % to 90 % and is highest among women attending STD clinics and college students, while being lowest among women in the general population. A similar analysis of 43 published studies from 1990 to 1996 was conducted to summarize the epidemiology of HPV among men [11]. Conversely, the prevalence of HPV in men reported among the studies assessed ranged from 1.3 % to 72.9 %, and the prevalence was >20 % in more than half of the studies that evaluated multiple anatomic sites. One important variation in gender prevalence is that there is not a good molecular HPV screening test for a man that is similar to the Pap smear or pelvic exam. In addition, in the clinical setting, male patients often seek medical care upon presentation of clinical findings, not as part of a screening protocol. This and the lack of objective testing are likely to falsely reduce prevalence estimates [12]).

Pathogenesis of External Genital Warts

One of the first questions that patients with EGW want to ask is not about how they grow, the prognosis with treatment, or about recurrence; patients want to know when they

were exposed so that they can go back in time to identify who was the source. The answer, often to the patient's disappointment, is typically very difficult to trace for them given the variability in the incubation times of the virus. A pivotal study from 2005 revealed that although genital warts routinely appear a median of 2.9 months from exposure, some can be visible within 2 to 3 weeks after exposure to the virus while others may not manifest for many more months or years [6•].

The process begins after microtrauma from sexual intercourse creates openings for the viral particles, primarily in thinner areas of mucosa, such as around the cervix and the anal verge. Incubation of HPV is based on hiding from the host immune responses. In addition, male patients that engage in anal sex may have more susceptibility in the perianal regions as well as anal mucosa given the associated trauma and resultant microtears. HPV particles are shed from the surface of the epithelium in dead and dying HPV-infected epithelial cells known as "koilocytes." These characteristic cells contain the infectious HPV genomes encased in the protein capsule. The inoculum of these cells into the traumatized areas of epithelium of a sexual partner creates the setup for migration of the virus to the basal keratinocytes. From there, the protein capsid must be shed before transfer of the HPV DNA. The ability to hide from the immune system originates here, because the lack of cell lysis and minimal viral replication in the basal layers results in no recognition of antigen available to immune surveillance of the host [13]. Latency is the hallmark of HPV, which is how the virus remains hidden from the host until the active phase of accelerated viral DNA replication in differentiating cells. The viral assembly of a protein capsule that envelopes the DNA core forms the infective unit. As the keratinocytes ascend through the now "infected" epithelium, shedding accelerates the process of transmission and the release of virus is not exposed to immune recognition [7••, 13, 14].

Unlike the herpes virus, which creates a brisk, host-inflammatory response resulting from ballooning degeneration and rupture of infected keratinocytes, there is no direct viral antigen presentation that would stimulate a dendritic cell effect to create a similar attempt at viral containment by the host [7••]. The ability of HPV to remain hidden inside keratinocytes and successfully evade host immune detection also is based on host immunocompetence, as patients with AIDS, solid-organ transplants, and relative sources of immunosuppression, such as smoking, iatrogenic agents, and even age, can be at higher risk of infection [15].

CDC Guidelines for Treatment for EGW

In 2010, an update on the guidelines for treatment of EGW was assembled by the Centers for Disease Control (CDC),

primarily focused on removal of the warts [16•]. The available therapies for external genital warts will likely reduce the infectious potential of HPV and clear the clinical lesions. However, eradication of the virus and a “cure” for HPV are not typically goals of therapy, because these endpoints cannot be proven [16•]. The preferred treatment options are individualized based on an effective balance between therapeutic efficacy, the side-effect profile, and the potential for maximum compliance. Therapy has to be based on the effectiveness of each treatment option for the number, extent, and location of the genital warts, as well as the convenience for the patient and patient preference [16•, 17]. The guidelines also suggest that because 3 months is usually an anticipated treatment endpoint, 3 months after treatment may be the first time to recurrence for most modalities [16•].

The CDC guidelines are divided into:

- 1) Provider-administered therapies: a) cryotherapy, b) podophyllin resin 10–25 %, c) trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90 %, and d) surgery.
- 2) Patient-applied therapies: a) podophyllin 0.5 % solution or gel, b) imiquimod 5 % cream (3.75 % cream is FDA-approved at a different dosage frequency but not mentioned in the guidelines), and c) sinecatechins 15 % ointment.
- 3) Other accepted therapies include: a) topical 5-FU cream, b) systemic or intralesional interferons, c) topical cidofovir, d) CO₂ laser treatment, e) electrosurgery, f) photodynamic therapy [5, 16•]

Origin of Catechins

Catechins are part of the polyphenol family, which are derived from their origins in the leaves of plants [18]. The derivatives include tannins, lignins, and flavonoids. The flavonoids are the best studied of the polyphenols and include many subtypes, including: a) flavonols, b) flavones, c) catechins, d) flavanones, e) anthocyanidins, and f) iso-flavonoids [19, 20••].

The therapeutic benefits of green tea are primarily due to the catechins, which are the most prevalent of flavonoids in green tea plants, known as *Camellia sinensis* [19, 20••]. Other common teas known to have therapeutic utilities, such as black tea and oolong tea, lose some content of catechins during the fermentation process due to the formation of oligomers caused by the oxidation of polyphenols. However, the catechin content in green tea leaves remains high, because fermentation of green tea is prevented due to a process of heating the leaves after they are picked [19, 20••]. The higher potency variant, epigallocatechin gallate (EGCG), is found in green tea but not black tea. During

black tea production, the catechins are converted to theaflavins and thearubigins [21]. In a high temperature environment, an epimerization change is more likely to occur, however, because exposure to boiling water for 30 minutes straight only leads to a 12.4 % reduction in the total amount of EGCG; the amount lost in a brief exposure is insignificant.

Therapeutic applications of catechins

The primary activities of catechins in green tea leaves are based on the effects of antioxidants, directed historically for the treatment of infectious diseases, cardiovascular diseases, neurodegenerative disorders, and cancer. These effects have several important therapeutic inflammatory benefits, which include:

- Scavenging reactive oxygen and nitrogen species
- Chelation of redox-active transition metal ions
- Inhibition of redox-sensitive transcription factors

These three processes are integral to the restoration of a healthy oxygen environment to reduce dermal stromal destruction, promote cellular immune functions and chemotaxis, as well as maximize direct cellular killing of viral-infected keratinocytes.

- Inhibition of pro-oxidant enzymes (e.g., nitric oxide synthase, lipoxygenases, cyclo-oxygenases, and xanthine oxidase)
- Induction of antioxidant enzymes (e.g., glutathione-S-transferases and superoxide dismutases) [20••, 22]

The proper balance of the activity of these enzymes allows for the enhancement of the other three effects listed above, especially the reduction of harmful free radicals.

In addition, the antiviral effects of catechins are based on suppression of the mechanisms impacting viral growth and replication. There are studies exemplifying these effects against influenza, adenovirus, and herpes simplex, although the main impact of action against HPV, human poxvirus, and other similar viruses remains theoretical.

Evidence supports the immunomodulatory effects of catechins that augment the role in the treatment of viral illnesses, such as warts, molluscum contagiosum, and other dermatoses, where the host immune response is unable to counter the infection. However, these are based primarily on the antioxidant effects. These effects are in contrast to the effects of imiquimod, which are based on the promotion of cellular immune responses, apoptosis, and other processes via binding and exertion of toll-like receptor 7 on dendritic cells [23].

Finally, more research elucidates the activity of sinecatechins on mechanisms that induce apoptosis against neoplastic

cells, including studies by Tyring et al. [24••], analyzing the growth inhibition of the sin catechins against HPV-infected cells isolated from a malignant cervical tumor. At variable concentrations, there was up to 50 % inhibition of the growth of several tumor cell lines, which was hypothesized to be due to the induction of tumor cell apoptosis via alteration of cell cycles. In addition, there may have been an antiproliferative effect that inhibited tumor growth. These observations may suggest that the sin catechins performed the following functions in this *in vitro* model [24••]:

- 1) Possible direct antiviral activity in the target cells
- 2) Antiproliferative activity in neoplastic cells
- 3) Promotion of apoptosis
- 4) Inhibition of telomerase (therefore limiting longevity of neoplastic cells and impeding tumor growth)
- 5) Activation of important transcription factors to down-regulate inflammatory mediators

Composition of Sin catechins Ointment 15 %

Sin catechins 15 % ointment is marketed in the United States as Veregen® (sin catechins) ointment 15 % and was approved by the FDA for the treatment of external genital warts in immunocompetent women and men aged 18 years and older. Of note, it is the first “botanical” product to receive FDA approval [25], providing a new answer for patients who are interested in a treatment that is considered “natural.” Historically, it was known as Polyphenon E when initially brought forward for study in Australia and other countries in 1999 by Medigene, who licensed the basic rights to the active ingredient in 1999 and then completed the clinical development of Veregen® as a proprietary drug. Subsequently, Medigene was responsible for bringing the drug successfully through the approval process [26]. Veregen® ointment is now distributed in the United States by Fougera, recently acquired by Novartis.

Of the sin catechins prepared in a proprietary quantified mixture of different catechins (85–95 % by weight) from green tea, the predominant catechin is epigallocatechin gallate (EGCg; comprising >55 % of the total content) [25]. The other three major catechins are epigallocatechin (EGC), epicatechin gallate (ECg), and epicatechin (EC) [24••], which are the most abundant catechins found in green tea extracts [20••]. Epigallocatechin gallate is the ester of epigallocatechin and gallic acid and *in vitro* shows the most potent effects of the catechin line. The other 45 % of sin catechins blend is comprised of the following [25]:

EGC	Epigallocatechin
ECg	Epicatechin gallate
EC	Epicatechin
GCg	Gallocatechin gallate

Cg	Catechin gallate
GC	Gallocatechin
C	Catechin

History

Veregen® 15 % ointment is manufactured via distinct processes in three countries (China, Japan, and Germany) before shipment for sale in the United States. Tea leaves are harvested and undergo an extraction process in China to obtain the starting material used in making the active pharmaceutical ingredient. The starting material is then shipped to Japan, where it is converted to the API via a proprietary enrichment process, which is then shipped to Germany where it is compounded into an ointment, filled into tubes, and packaged for shipment to the United States [25]. Veregen® is already available to patients with external genital warts and other indications in Germany, Austria, and Spain, and outside the EU, Veregen® has been approved in Switzerland, Israel, and Serbia. Applications for approval have been submitted in further countries [26].

The majority of research and scientific work as well as potential clinical applications were initiated in Australia, under the name Polyphenon E, which is under the trademark that the initial manufacturer, the Mitsui Norin Co., Ltd. of Japan, applied to their family of green tea polyphenol extracts [27].

Clinical Trial History of Polyphenon

One of the first pivotal studies to evaluate the efficacy of green tea-extracted polyphenols was performed in Germany and published in 2008 [21]. This study examined 503 patients randomized to receive Polyphenon E 15 % or 10 % ointment or matching vehicle, applied by the patients three times daily to all warts. Biweekly assessments of response and of adverse events was performed until complete clearance of all (baseline and new) anogenital warts or for up to 16 weeks, and the potential of recurrence was evaluated during a 12-week, treatment-free, follow-up period. The study revealed that 53 % of patients treated with Polyphenon E 15 % ointment showed complete clearance of all baseline and new anogenital warts, 51 % for Polyphenon E 10 % ointment compared with 37 % for the patients in the vehicle arm. There were several important observations made in the study:

- 1) Women responded better than men; approximately 60 % of women and 45 % of men in both active groups achieved complete clearance of all warts.
- 2) The time to complete clearance was comparable for both strengths of Polyphenon E ointment; approximately 78 %

of all patients treated with Polyphenon E 15 % or 10 % ointment showed wart clearance rates ≥ 50 %.

- 3) Fewer than 6 % and 4 % of patients in the Polyphenon E 15 % and 10 % ointment groups reported a recurrence.
- 4) The majority of all adverse events were local application site reactions [28•].

Similar to imiquimod 5 % cream, which was originally brought to market for external genital warts, a phase II trial of Polyphenon® E Ointment (15 %) for the treatment of actinic keratosis was conducted that enrolled a total of 62 patients, 42 of which received Polyphenon® E ointment and 20 received placebo ointment for a course of 4 months. The primary endpoint was reduction of the number of visible skin lesions in a selected area of the scalp or face, although there was no mention of other study parameters given that it was not a phase III trial. It was noted that after treatment with Polyphenon® E Ointment, there was a significantly higher number of the remaining visible lesions than at baseline, suggesting that the immunomodulatory properties of Polyphenon® E helped to demonstrate clinically subclinical lesions. However, the chosen treatment regimen and trial length was not sufficient for complete healing of all lesions [28•]. As a result, the dosage plan successfully applied to the treatment of genital warts could not be transferred to the treatment of actinic keratosis [29].

In 2000, a randomized, double-blind, placebo-controlled, phase II trial (clinical trials NCT 00005097) was initiated at several sites to evaluate the efficacy of a similar polyphenol-based compound as a treatment for actinic keratosis [30]. The focus of the trial was to show treatment efficacy in patients and clearance against endpoints of the “pathobiology of actinic keratosis.” However, according to www.clinicaltrials.gov, this trial was “terminated due to the low conditional power for a positive study” [30].

Phase III Trials for EGW

Two pivotal trials were performed that were published to elucidate the success of sinecatechins ointment 15 % for the treatment of external genital warts. One of the studies was conducted primarily in Europe, as well as in South Africa, as part of the same study with polyphenon E ointment published in 2008. The other was conducted primarily in North America and with one study site in Romania [28•, 31•]. Unlike previously approved patient-applied therapies for genital warts, which used clearance of baseline warts as the study endpoint, these trials defined clearance as complete clearance of *all* baseline warts and new warts that developed during the treatment period [28•, 31•, 32•].

The enrollment criteria were limited to female and male patients, aged 18 years or older (including females of

childbearing age and potential), diagnosed with 2 to 30 warts with a total wart area of 12 mm² to 600 mm² involving primarily genital surfaces [28•, 31•, 32•]. Patients with skin of all pigmentation types were included. There was a primary endpoint of complete clearance of all warts at baseline as well as any new lesions demonstrated during the study. Secondary endpoints included time to complete clearance, assessment of partial clearance, local signs and site reactions, recurrence of any cleared wart, and occurrence of new warts 12 weeks posttreatment. In each trial, ointment was applied TID for up to 16 weeks. The treatment period was followed by a 12-week, treatment-free period to assess for recurring warts.

The result of the study showed that complete clearance of all EGW was obtained in 53.6 % of all patients treated with Veregen® ointment: 15 % (n=397) versus vehicle (35.3 %; n=207). In addition, the female arm demonstrated higher clearance rates (60.4 % versus vehicle 43.8 %) following therapy compared with males (47.3 % versus vehicle 28.8 %). Overall, 56 % of treatment-naïve patients experienced complete clearance; however, approximately 43 % of patients who had one or more prior episodes of EGW experienced complete clearance of all EGW after treatment [28•, 31•, 32•]. Although complete clearance was seen as early as 2 weeks in some patients, it was significantly greater with the active ingredient compared with vehicle beginning at week 6. Finally, among the 53.6 % of Veregen® patients with complete clearance, 6.8 % experienced recurrence at 12 weeks posttreatment [24•, 32•]. Among the 35.3 % of vehicle patients with complete clearance, 5.8 % experienced recurrent warts at 12 weeks posttreatment [24•, 32•]. The investigators theorized from the data and their observations that the low recurrence rate in the vehicle group may result from the keratolytic activity of the vehicle formulation, which would induce an inflammatory response that could facilitate skin healing and sustained clearance [32•].

The patients' experiences were evaluated during the trials. In these trials, 397 patients received Veregen® ointment 15 % and 207 received vehicle TID for up to 16 weeks in the phase III clinical studies. Application-site reactions, such as pruritus, erythema, burning, pain, ulcer, edema, and induration, occurred in 341 of 397 (86 %) in the treatment group and 136 of 207 (66 %) in the vehicle groups.

Conclusions

The potential applications of this class of treatments are expansive based on the understanding of the immune mechanisms involved as well as the safety profile. Although there is currently not any clinical trial data or publication in the literature, the utility for catechins and polyphenol-based

conditions similar to *Condyloma acuminata* is basically intuitive. Patients with diseases, such as molluscum contagiosum, verruca planae, and even common warts, which currently lack an FDA-approved therapy, may possibly benefit from this line of therapies given the usual patient ages involved, the locations on the body, and the high likelihood of previous treatment failures. Although previous trials using polyphenols for the treatment of actinic keratosis, basal cell carcinoma, and other benign and malignant tumors have not successfully led to an accepted treatment regimen, the elucidation of new formulations and potencies may possibly create another option for topical management as either adjuncts or alternatives to surgery.

For its currently approved indication, sinecatechins 15 % ointment is a useful and safe option for the treatment of external genital warts for patients aged 18 years and older. Patients with multiple lesions, multiple surface areas involved, and who otherwise are candidates for topical therapies are currently experiencing the benefits of this compound either as monotherapy or as part of a combination regimen with office-based destructions. However, these therapies are only successful when combined with the education and screening of sexual partners, incorporation of safer sexual practices, and the early recognition of initial and recurrent presentations.

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