Current Best Evidence

Current best evidence from dermatology literature

Tatti S, Stockfleth E, Beutner KR, Tawfik H, Elsasser U, Weyrauch P, Mescheder A. Polyphenon E®: a new treatment for external anogenital warts. Br J Dermatol. 2010;162:176–184.

External genital warts (EGWs) are contagious, nonmalignant, squamous cell tumors caused by infection with the human papillomavirus (HPV), most commonly types 6 and 11, and their incidence is on the rise. Treatments may be patient-administered (e.g., imiquimod, podophyllotoxin) or physician-administered (e.g., cryotherapy, curettage, trichloroacetic acid, and laser surgery). All these therapies may be associated with considerable side effects and high recurrence rates. New and improved treatments for EGWs are therefore needed.

Polyphenon E® (MediGene AG, Martinsried, Germany) is a standardized extract of green tea leaves from *Camellia sinensis,* containing mainly tea polyphenols, mostly consisting of catechins (> 85%), which are believed to possess immunostimulatory, antiproliferative, and antitumor properties. Immunostimulatory activity is believed to be due to proinflammatory cytokines (e.g., IL-1, IFNγ, TNFα). Imiquimod acts similarly by inducing the synthesis of cytokines IFNα, IL-1, IL-6, and TNFα, by activating cells via a toll-like receptor 7 (TLR7). The aim of this study is to obtain more precise data on the efficacy and safety of Polyphenon E® ointment, by integrating the findings of the two previous phase III trials by the same group of authors. Patients aged ≥ 18 years (n = 1005), with 2 – 30 EGWs (12 – 600 mm^2 total area) were asked to apply vehicle (GVeh; n = 207), Polyphenon E® ointment 10% (G10%; n = 401) or Polyphenon E® ointment 15% (G15%; n = 397) thrice daily until total clearance or a maximum of 16 weeks.

Complete clearance of all EGWs was obtained in 53.6% (G10%) and 54.9% (G15%) of the patients with Polyphenon E® versus 35.4% in vehicle group ($P < 0.001$). Chance of complete clearance was two-fold higher and time to complete clearance was shorter in the active treatment groups ($P < 0.001$). Recurrence rates over a 12-week follow-up were low and similar across groups: 5.8, 6.8, and 6.5% (GVeh, G10%, and G15% groups), respectively. Local reactions including erythema, edema, erosion, and local skin symptoms were observed in 86.2% and 81.5% of the patients in the G10% and G15% groups, respectively. However, severe reactions were only rarely reported (1.5%, 9.2%, and 13.5% for GVeh, G10%, and G15% groups, respectively).

Comments: Most treatment modalities for EGWs are physician-administered and need repeated visits to the clinic at frequent intervals, which is inconvenient for the patients. Among the self-administered treatments, imiquimod 5% cream and podophyllotoxin have comparable efficacy to polyphenon E, but relatively higher recurrence rates ranging from 13 to19% and up to 91%, respectively. The authors report a high efficacy in the clearance of EGWs compared to vehicle alone, with both concentrations (10 and 15%) showing almost equivalent efficacy. The authors also mention that the complete and partial clearance rates are higher and recurrence rates lower than those of other self-administered treatments. The latency of HPV infection is long; therefore, the 12-week follow-up period in this study may have not been long enough to detect the persistent effects of Polyphenon E®. The withdrawal rates were 17.2% and 19.4% for the G10% and G15% groups, respectively. One of the causes may be poor compliance because of the need of thrice daily application, which may be slightly inconvenient compared to the usually prescribed thrice-a-week application of podophyllotoxin and imiquimod. Local reactions are common in the treatment groups. It is believed that the local reactions to medication are due to the immunostimulatory effects of the catechins, which are essential for achieving a clinical response. The authors have also found that complete clearance correlated statistically and significantly with erosion or ulceration and erythema objectively assessed by the investigators. To conclude, treatment with Polyphenon E® ointment may offer a valuable addition to the current therapeutic options against a common, but difficult-to-treat clinical problem.

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Templeton DJ, Jin F, McNally LP, Imrie JC, Prestage GP, Donovan B, Cunningham PH, Kaldor JM, Kippax S, Grulich AE. Prevalence, incidence and risk factors for pharyngeal gonorrhea in a community-based HIV-negative cohort of homosexual men in Sydney, Australia. Sex Transm Infect 2010;86:90-96.

Pharyngeal infection with *Neisseria gonorrhoeae* has been recognized since long and is especially common among men who have sex with men (MSM) in both community- and clinic-based settings. In fact, recent studies suggest that the pharynx may be the most common site of gonococcal infection in MSM. However, there are no community-based studies on the proportion of pharyngeal gonorrhea, which occur independent of the anogenital infection. It is known that gonococcus is more efficiently transmitted via fellatio than cunnilingus and the high incidence of pharyngeal gonococcal infection among MSM may be because of the high prevalence of oral sexual behaviors in this population. From 2003, the authors recruited all participants in the Health in Men cohort of the HIV-negative homosexual men in Sydney and performed annual pharyngeal gonorrhea screening, using the BD ProbeTec nucleic acid amplification (NAAT) assay, with supplementary porA testing. Detailed sexual behavioral data were collected every six months and a note was made of the participants' self-reported pharyngeal gonorrhea. Among 1427 participants, 223 pharyngeal samples tested positive with the BD ProbeTec assay, out of which 65 pharyngeal gonorrhea infections reactive on both BD ProbeTec assay and LC porA assay were identified (incidence 1.51 per 100 person-years, PY). The combined incidence of pharyngeal gonorrhea when including study visit-diagnosed and self-reported infections was 4.45 per 100PY. This was higher than the incidence of anal and urethral gonorrhea in the same population. Most patients (84.6%) diagnosed with pharyngeal gonorrhea did not have concurrent anal or urethral gonorrhea. Risk factors identified were younger age ($p = 0.001$), higher number of male partners ($p = 0.002$), and history of contact with gonorrhea ($p < 0.001$). Among sexual behaviors, insertive oro-anal sex ('rimming') was the only one independently associated with pharyngeal gonorrhea. No association of pharyngeal gonorrhea with pharyngeal symptoms in the previous week was observed.

Comments: There are few incidence data on pharyngeal gonorrhea infections among homosexual men. One other community-based study has reported a higher incidence, of 11.2 per 100 PY among HIV-negative MSM. However, in that study only the BD ProbeTec assay was used, without supplemental gonococcal NAAT testing. The BD ProbeTec assay used alone has a lower positive predictive value. Relying solely on the BD ProbeTec assay can lead to a substantial overestimation of gonorrhea incidence. This study as well as the previous studies report that gonococcal infection of the pharynx among MSM occurs more frequently without concurrent anogenital infection. This is in contrast to anogenital gonorrhea, where over one-third of the study participants have gonorrhea infections simultaneously diagnosed at other sites. Moreover, the incidence of pharyngeal gonorrhea is higher than that of urethral or anal gonorrhea, which may be explained by the relatively lower prevalence of unprotected anal sex as compared to unprotected oral sex. As there has been no association of pharyngeal gonorrhea with pharyngeal symptoms in the previous week, it may be difficult to suspect gonorrhea on the basis of clinical symptoms of sore throat alone. Several studies have reported an independent association of receptive penile-oral sex with pharyngeal gonorrhea infection among MSM. However, the association of pharyngeal gonorrhea with insertive oro-anal sex reported here has not previously been described or investigated prospectively. This can be attributed to the fact that gonococcus is detected more frequently in the anus than in the urethra of MSM. The strengths of this study include the strict diagnostic criteria by using both BD ProbeTec assay and LC porA assay and reporting both study visit diagnosed and self-reported pharyngeal gonorrhea.

To conclude, this study reveals that the incidence of pharyngeal gonorrhea among MSM may be higher than previously reported and insertive ano-oral sex is the only significantly associated sexual practice. Pharyngeal gonorrhea often being asymptomatic may serve as a reservoir of infection among MSM and may go undetected unless specifically screened for and treated, in order to decrease the prevalence of gonorrhea .

Mirmirani P, Karnik P. Lichen planopilaris treated with a peroxisome proliferator-activated-receptor γ agonist. Arch Dermatol. 2009;145:1363-6.

Lichen planopilaris (LPP) is a primary cicatricial alopecia characterized by patchy or diffuse hair loss with perifollicular erythema and scaling at the margins. Treatment options include topical and intralesional corticosteroids, oral antibiotics, hydroxychloroquine sulfate (HCQS), oral prednisolone, mycophenolate

mofetil (MMF), cyclosporine, and so on. The authors report a case of LPP in a 47-year-old man with longstanding, androgenetic alopecia who presented with a sudden onset of scalp irritation, redness, and rapid hair loss. Cutaneous examination revealed male pattern baldness in combination with scattered patches of hair loss, with absent follicular markings in the center, and perifollicular scaling and erythema in the periphery. Scalp biopsy findings were consistent with LPP. Over the next 1.5 years the patient was treated with numerous regimens including oral prednisone, HCQS, oral doxycycline, MMF, intralesional and high-potency topical corticosteroids, topical tacrolimus, and ketoconazole shampoo. He declined treatment with cyclosporine. Although there was mild improvement in the symptoms and signs, his scalp itching persisted, as did perifollicular scaling and erythema, and a repeat biopsy revealed a decreased, but persistent inflammatory infiltrate. The patient was started on peroxisome proliferator-activated receptor γ (PPARγ) agonist, pioglitazone hydrochloride, and 15 mg/d orally, while he continued to use ketoconazole shampoo. The medication was tolerated well and the patient reported significant improvement in the scalp itching. Examination at a two-month follow-up revealed a decrease in the patient's recorded symptoms and signs clinically. Scalp biopsy at six months revealed a dramatic decrease in the inflammatory infiltrate. The patient continued to take pioglitazone for eight months, and on a one-year follow-up he continues to be symptom-free without evidence of inflammation or further hair loss on examination.

Comments: Of late, studies in mice have revealed that target deletion in PPAR- γ, in the follicular stem cells causes hair loss and skin changes resembling lichen planopilaris. The authors, in a previous study have also shown that the expression of genes required for lipid metabolism and peroxisome biogenesis are decreased in LPP, specifically dramatically downregulated expression of PPAR- γ. These data support the concept that PPAR- γ is essential for healthy pilosebaceous units and this has led to a new model for the pathogenesis of cicatricial alopecia, in which a loss of PPAR- γ function leads to decreased peroxisome biogenesis and lipid homeostasis, causing damage to the pilosebaceous unit, which triggers inflammation and lipoapoptosis causing cicatricial alopecia. Based on these findings, the authors present a novel strategy for the management of LPP, using PPAR γ agonist pioglitazone. Studies assessing the efficacy of topical PPAR- γ agonists are ongoing. Although glitazones seem to be primarily safe medications, there is a risk of peripheral edema due to fluid retention, and there are reports of increased risk of myocardial infarction and congestive heart failure in patients with risk factors. Hence, the authors suggest cautious use in patients with cardiovascular disease. It is also suggested that liver function tests be obtained before and during therapy.

Haeck IM, Hamdy NA, Timmer-de Mik L, Lentjes EG, Verhaar HJ, Knol MJ, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Low bone mineral density in adult patients with moderate-to-severe atopic dermatitis. Br J Dermatol. 2009;161:1248-54.

Atopic dermatitis (AD) is a common inflammatory skin condition that may theoretically lead to increased risk of osteopenia and osteoporosis due to chronic inflammation and concomitant use of corticosteroids. The aim of this study is to assess the prevalence of osteoporosis and osteopenia in adult patients with moderate-to-severe AD and to study the association of bone mineral density (BMD) with topical / oral corticosteroid use and disease activity. BMD was measured at the lumbar spine and hips using dual-energy X-ray absorptiometry in 125 adult patients (64 men and 61 women; aged 16 – 82 years) with moderate-to-severe AD. The cumulative dose of topical and oral corticosteroids was calculated and lifestyle parameters were collected by using a questionnaire. Serum concentration of thymus and activation-regulated chemokine (TARC) were also measured. The authors used the WHO definitions for osteoporosis (decrease in BMD by 2.5 SD or more below the average) and osteopenia (T-score between -1 and -2.4 SD). A Z-score ≤ -1 was defined by the authors as low bone mineral density (BMD). Six patients (4.8%) had osteoporosis, while 41 (32.8%) had osteopenia. Low BMD was seen in 30.4% of the patients, with more men (43.8%) than women (16.4%) affected. Alcohol, coffee and dairy product intake, smoking, exercise, sunlight exposure, use of contraceptives or menopausal status, and the common confounding factors, were not significantly different between the patients with low and high BMD. No significant association was found between low BMD and the biochemical parameters of bone metabolism, serum TARC levels, and the cumulative dose of topical and oral corticosteroids during the five years, prior to inclusion. The authors documented low BMD in approximately one-third of the patients with moderate-to-severe AD, independent of the five-year cumulative dose of corticosteroids, which may

implicate the role of the chronic inflammatory process in osteopenia.

Comments: This is probably the first study documenting low bone mass in adults with AD. The results show a low prevalence of osteoporosis, but a high prevalence of osteopenia and around one-third of the patients showed low BMD. The prevalence of low BMD was found to be higher among men than women. Surprisingly the study did not reveal any significant difference in the total cumulative dose of topical and / or oral steroids used by patients of low and high BMD. However, using logistic regression analysis, it was found that there was a trend, although statistically insignificant, toward an increased risk of low BMD, with higher use of topical and oral corticosteroids.

As higher disease severity leads to a higher consumption of topical and even oral corticosteroids, these factors are highly related and cannot be separated because of the lack of a good measure of chronic disease severity. Serum TARC level is an objective marker of disease activity during an exacerbation and there has been no correlation between the serum TARC levels (and hence disease activity) and BMD. Similarly, the BMD does not correlate with the markers of cumulative bone resorption and formation, including serum RANKL, OPG or RANKL / OPG ratio. There is also no significant correlation between the absolute value of BMD and serum 25-hydroxyvitamin D levels.

The question of whether the deleterious effect on bone mass observed in patients with AD is due to the intensity of topical corticosteroid use over a longer period of time, that is, beyond a five-year assessment period, to the underlying inflammatory process or due to a combination of both remains to be established. Based on the results of this study, the authors advocate the measurement of BMD in patients with moderate-to-severe AD, particularly in men, to allow the detection of patients at increased risk for skeletal morbidity.

Ryder N, Jin F, McNulty AM, Grulich AE, Donovan B. Increasing role of herpes simplex virus type 1 in first episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992–2006. Sex Transm Infect. 2009;85:416-9.

It is known that herpes simplex virus type 1 (HSV-1) is causing an increasing proportion of anogenital herpes, however, it is not clear which populations are predominantly affected.

No time-trend data on the proportion of the first-episode anogenital herpes that includes the type, anatomical site, and gender of sexual partners exists currently. This study is a retrospective analysis, wherein cases of first-episode anogenital herpes have been identified from the electronic database of the Sydney Sexual Health Center, from 1992 to 2006.

The cases were defined as microbiologically confirmed cases with anogenital lesions of herpes. The cell culture was the microbiological confirmation until August 2004, after which a polymerase chain reaction assay was used. Between 1992 and 2006, clinically defined anogenital herpes was seen in 4440 patients, of whom 1845 (42%) were microbiologically confirmed to be with HSV and 653 (35%) of these were HSV-1. There was an increase in the overall proportion of cases due to HSV-1 from 29% in 1992 – 1994 to 42% in 2004 – 2006 (OR per three-year band 1.19; 95% CI 1.11 to 1.27). This increase over the years reached statistical significance only among heterosexual women (p trend < 0.01). Overall, MSM (52%) were more likely to have first-episode anogenital herpes due to HSV-1 than heterosexual men (27%) or women (37%) and equally likely as women having sex with women (48%). First episode anal herpes patients had a higher proportion of cases due to HSV-1 compared with genital herpes (48% vs. 34%). Over time, the increasing proportion of first-episode anogenital herpes due to HSV-1 remained significant even after adjustment of the anatomical site, age, and gender of sexual partners. When the analyses were stratified by age, this increasing trend was only significant in younger MSM (OR 1.58) and younger heterosexual women (OR 1.30). No significant increasing trend was found in patients older than 28 years.

Comments: In this study the authors have demonstrated that the proportion of first-episode anogenital herpes due to HSV-1 increased significantly between 1992 and 2006, particularly in younger MSM and among heterosexual women. Two mechanisms may be responsible for the shift toward HSV-1: (1) a reduction in the acquisition of HSV-1 during childhood leading to increased susceptibility in young adults, and (2) an overall or relative increase in the incidence of oral sex. Studies in the US and UK have demonstrated a 14% decrease in HSV-1 seroprevalence in individuals younger than 20 years and children aged 10 – 14 years, respectively. Other studies have found an association between recent oral sex and symptomatic genital HSV-

1 infection. This study has also found an increase in the prevalence of oro-anal sex between MSM.

The findings of this study have significant clinical and public health implications. Among MSM and young women, in whom HSV-1 may be responsible for a significant proportion of cases of anogenital herpes, it is important to order type-specific testing so as to be able to counsel about prognosis, as anogenital herpes caused by HSV-1 has a much lower chance of recurrence and subclinical shedding compared to HSV-2. Vaccines for prevention of anogenital herpes would require protection against HSV-1 as also HSV-2.

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