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Enhanced Treatment Strategies for External Genital Warts

Montreal - External genital warts (GWs) are the most common sexual health disorder for which young men and women seek medical attention and, globally, more cases and recurrent episodes are being reported. GWs are associated with considerable psychological distress and potentially very unpleasant and painful treatment. Although the natural history of GWs suggests that most patients will eventually clear the warts, treatment with an immune response modifier may accelerate the natural immune response and hasten clearance. Current treatment with the immune response modifier imiquimod 5% is recommended for up to 16 weeks but experience with a new imiquimod formulation suggests that patients can achieve good results in half that time. The shorter treatment regimen may improve compliance, leading to better outcomes.

It is estimated that approximately 75% to 80% of sexually active men and women have been exposed to genital human papillomavirus (HPV). Types 6 and 11 are the cause of most cases of genital warts (GW) worldwide (*J Am Osteopath Assoc* 2006;106(3 suppl 1):S2-S8). The psychosocial burden associated with GWs is high. In PISCES (Psychosocial Impact of Cervical Screening and Condylomas: An Epidemiological Study), for example, Canadian investigators found that a greater proportion of women with a first episode of GWs at 67% reported some degree of anxiety or depression compared with 32% of controls (Abstract P-548). Several health domains were also adversely affected for both men and women with a first or recurrent episode of GWs. The negative impact of GWs on all outcomes of health-related quality of life was maintained as long as the lesions persisted.

As discussed here at the HPV conference by Dr. Marc Steben, Chief, Sexually Transmitted Diseases, Institut national de santé publique du Québec, Montreal, most patients with a healthy immune system clear GWs at a median of 125 days after initial appearance. On the other hand, "whatever we do to kill the lesion, we are not addressing the virus," he remarked. The only treatment that may prove the exception to this is immune stimulation with an agent such as imiquimod. As an immune response modifier, it appears to accelerate the natural immune response needed to clear GWs.

As Dr. Steben noted, treatment of GWs depends on where the lesions occur. "We also have to be careful not to cause scarring that might obstruct urinary flow and make sure that treatment or its consequences are not worse than the natural history of having GWs," he cautioned. Treatment may also be associated with considerable discomfort and frank pain, as Dr. Steben also noted, along with erythema, epithelial erosion, ulceration, depigmentation and scarring. Among expert-recommended self-applied treatments for GWs is imiquimod cream 5%. Usually, patients apply a thin layer of the cream three times a week with at least one day off in between doses for up to 16 weeks.

Lower Concentrations, Shorter Treatment Schedule

Results presented here investigating two new formulations with lower concentrations of imiquimod demonstrated success within a shorter treatment duration while maintaining similar efficacy to the 5% formulation. In two phase III randomized studies led by Dr. Daron Ferris, Medical College of Georgia, Augusta, daily applications of imiquimod 2.5% and 3.75% for up to eight weeks were compared with placebo. Patients were instructed to apply up to 1 packet (250 mg cream) of either imiquimod 2.5%, 3.75% or placebo daily until complete clearance of all (baseline or new) warts, or up to a maximum of eight weeks. Clearance was defined as 100% clearance of all baseline and newly emergent warts in all anatomical areas treated. For those who achieved complete clearance at the end of eight weeks, there was an additional 12-week follow-up.

The study population were difficult-to-treat patients: they had a mean disease duration of 4.9 years and 52% had ≥ 1 anatomical area to treat. A total of 260 patients assigned to imiquimod 2.5% completed the study, as did 285 patients in the 3.75% group and 143 placebo controls. At study onset, the mean number of lesions was similar in both active drug arms at 8.4 and 8.6 for the 2.5% and 3.75% creams, respectively, and slightly higher at a mean of 9.6 lesions with placebo. The mean wart area ranged from a low of 150.4 mm² in the 3.75% cream group, 160.7 mm² in the 2.5% cream group and 171.9 mm² in placebo patients.

Roughly 70% of participants received treatment for their first GW episode even though the mean duration of disease was 4.9 years. A slightly greater proportion of women than men were enrolled in the studies although the proportions of each gender were very similar in each treatment arm.

At the end of the eight-week trial, the intent-to-treat (ITT) analysis showed that complete clearance was achieved in 28.3% of the imiquimod 3.75% group, 22.1% of the 2.5%

group and 9.4% of placebo controls ($P < 0.001$ vs. placebo). In the per-protocol analysis, corresponding clearance rates were 33.8%, 27% and 11.5%, respectively. At least a 75% reduction in wart count was achieved in 45.9%, 36.3% and 13.4% at the same follow-up interval ($P < 0.001$ vs. placebo). The mean per cent change in lesion reduction from baseline was 51.4%, 41.2% and 6.7%, respectively ($P < 0.001$ vs. placebo) (Figure 1).

Figure 1. Mean Reduction in Wart Count (per protocol)



P values are from Cochran-Mantel-Haenszel test taking 2 treatment groups at a time.
*Statistically significant by Hochberg's modified Bonferroni procedure ($P \leq 0.025$).

Adapted from Ferris et al 26th IPV. Poster P-544.

Response was also considerably higher in females, as investigators pointed out, with 43.1% of females treated with the 3.75% cream in the per-protocol analysis achieving complete clearance at study end point compared with 22.7% of males. The authors suggested that the higher efficacy seen in females might reflect gender differences in skin keratinization of treated anatomic locations.

Reductions in wart count were also greater in females: 56.2% of those assigned to the 3.75% formulation reported at least a 75% reduction in wart count compared with 33.6% of males, again based on the per-protocol analysis. Among those participants who entered the 12-week follow-up, 69.6% of the 3.75% group ($n=102$) reported sustained complete clearance.

Seventeen treatment-emergent serious adverse events (AEs) were documented in 12 subjects but none were considered related to study drug by the investigators.

Treatment-related AEs were reported for 17.5% of the 3.75% imiquimod-treated patients, 16.9% of the 2.5% imiquimod group and 2.5% of the placebo group. A rest from treatment was required for 31.5% of the 3.75% group, 27.4% of the 2.5% group and 2.0% of the placebo group. As the authors concluded, imiquimod 3.75% cream, dosed daily for up to eight weeks, fulfills a need for a shorter and simpler treatment regimen for GWs. It provides clinically meaningful benefit with respect to complete clearance of all warts and in reduction in wart counts, with an acceptable safety profile.

Ease of Application

Dr. Steben observed that findings from a phase IV trial he reviewed several years ago showed that the immune response modifier was by far the preferred treatment for GWs over any other therapy. The reason for this preference, he suggested, is its ease of application compared with other home-applied therapies. "You put imiquimod on your finger and you can apply the cream directly on the lesion whereas with other therapies, you have to put the product on a cotton applicator or a plastic spatula and it is quite difficult to hold the bottle, the mirror, and the light and spread the product, especially for patients who have limited mobility or who are obese," he explained.

For patients who have chronic warts—a sign that their immune system may not be robust enough to clear the warts as well as for smokers, as smoking compromises immune function—imiquimod may also be a good choice. Dr. Steben indicated that it may also be used to treat patients who have very large quantities of warts prior to debulking surgery. He added, "For those patients I mainly see who have failed regular therapy and who have been in treatment for years, these patients are usually prescribed ablative therapy in the office and imiquimod at home."

Summary

GWs have a negative impact on health-related quality of life outcomes with a high psychological burden. There is a need to treat GWs as effectively and conveniently as possible and hasten clearance. Once-daily application of the immune response modifier imiquimod at a lower 3.75% concentration for up to eight weeks has been proven effective and the shorter treatment interval may help improve patient adherence and thus clearance of GWs. □

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