The Role and Actions of Imiquimod, the New Immune Response Modifier for Genital Warts

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Introduction

Anogenital wart (AGW), a manifestation of human papillomavirus (HPV) infection, is a sexually transmitted disease commonly come across in all races and socioeconomic groups world-wide. In most parts of the world, about 1% of adults has visible genital warts. In USA and most European countries, 2-4% of the Papanicolaou smear shows cytologic evidence of HPV infection. With more sensitive techniques such as southern blot and polymerase chain reaction, an even higher prevalent rate (10-40%) can be detected. Besides producing disfiguring and warty growths that impose a cosmetic concern to the patient, HPV infection is associated with cervical cancer, though penile and vulval cancers rarely happen in immunocompetent patients. Therefore, it is cost-effective in treating external anogenital warts to prevent the spread of infection, decrease the occurrence of genital carcinoma and relieve psychological burden of patients.

Wart therapy

Patient education and counseling is important before treatment. Patients must be well informed of the infectious nature of AGW, its transmissibility and the association with cervical cancer, so that surveillance upon themselves and their partners can be carried out. The high chance of recurrence and therefore difficulty in treatment should also be emphasised.

Modalities of treatment

Chemical destruction

It includes the trichloroacetic and bichloroacetic acids (TCA/BCA), podophyllin, and the self-applied podofilox gel. Besides eliminating the growth, this form of treatment may alert body immune system by exposing the virus when cells being lysed by the chemicals. Treatment is usually well tolerated, but marked reaction including irritation and erosion is not infrequently seen with podophyllin.

Physical destruction

It includes cryotherapy, electrocautery and laser therapy. It works fast but excessive skin destruction may result in scarring. Furthermore, the recurrence rate is high.

A decade ago, aggressive therapy for AGW was advocated. However, there is increasing evidence illustrates that aggressive treatment do not change the course of the cervical disease once it is established. Virus cannot be eliminated by aggressive treatment and its transmissibility cannot be reduced. Besides, treating partners does not prevent recurrence of their own. Therefore, a conservative approach should be adopted. Recommendation from CDC, 1993 is as follows:

"Expensive therapies, toxic therapies and procedures that result in scarring, should be avoided. The goal of treatment is the removal of exophytic warts and amelioration of symptoms and signs but not eradication of HPV."

With this concept, the enhancement of host immunity is the latest trend of therapy. The use of Interferon-alpha (Intron A, Alferon N) in AGW was intensively studied in 1980s, and in recent years a new medication, imiquimod, emerges.

Immune-response modifier

A representative study in treatment of AGW with interferon alpha-2a was conducted by Eron et al. 257 patients were recruited in the study and about half of them received interferon. One to three warts of each patient were injected intralesionally with interferon 10^6 *iu*/injection up to nine injections. Frequent systemic side effects limited the number of injections. At the end of study, 36% of the warts were cleared in the interferon group whereas 17% of the warts were cleared in the placebo group. However, there was quick relapse after cessation of treatment.

Imiquimod (IQ) is another immune-response modifier. Though it has no direct antiviral or antitumour activity in vitro, these activities can be induced and

enhanced by the drug in vivo. It stimulates monocytes/ macrophages and dendritic cells to produce cytokines. Alpha-interferon is produced first, followed by tumour necrosis factor (TNF), interleukin-1B (IL-1B), IL-6 and IL-8. The cytokines in turn stimulate T cell, activate NK cells and stimulate B cells to divide and produce cytokines of their own. B cells can also enhance Th1 antibody production (IgG2a) and cytokines release. On the other hand, they inhibit Th2 antibody production (IgE), release of other cytokines such as IL-2 and reduce eosinophilia.

A multi-centre, vehicle-controlled trial evaluating the safety and efficacy of 5%(IQ5%) and 1%(IQ1%) imiquimod cream in patients with external genital/ perianal warts had been reported. The dosing regimen was an eight hour application overnight, three times per week until clearing or up to 16 weeks. There were 311 patients recruited (180 males and 131 females). They were greater than 18 years of age, having two to fifty AGW with individual wart area larger or equal to10mm^2. Immunocompromised patients, those with major organ dysfunction, prior treatment with antiviral, immune modulating medication or wart therapy were excluded. Approximately equal number of patients were randomised to either IQ 5% group, the IQ 1% group, or the vehicle control group (109,102 and 100, respectively). At the end of 16 weeks, wart clearance rate was 77% for females in the IQ 5% treatment group and 20% for females in the vehicle group; for males, the clearance rate was 40% in the IQ 5% treatment group and 6% in the vehicle group. The differences were statistically significant. The median time for clearing was eight weeks in females and 12 weeks in males. The higher clearance rate in females can be due to better absorption through thinner and moisturised skin in females. Another reason may be that they presented to clinics earlier than men. Warts that have been present for longer period of time before therapy appear to be more resistant to treatments than newly developed warts. It is also possible that part of immune system is more active in women. Among all the possible local side effects (including erosion, flaking, edema, scabbing, induration, ulceration and vesicles), erythema was the commonest (27% mild, 34% moderate, and 5.7% severe). The local reactions usually occurred early at the start of therapy and improved later during the study or temporary cessation of therapy. No systemic absorption could be demonstrated by measuring serum/ urine levels. Those patients with cleared warts were followed up biweekly for 3 months. Recurrence of warts happened in 13% of IQ 5% group, 0% of IQ 1% group and 10% of the vehicle-group. The recurrence rate is not high when comparing to other modalities of treatment.

Treatment of AGW	Efficacy %	Recurrence rates %
IQ 5%	40-77	13
Interferon-alpha	36-62	21-25
Podofilox gel	45-88	35-60
Podophyllin	22-80	30-60
TCA/BCA	<80	30-60
Cryotherapy	69-70	45
Laser	100	9-72

There was another study investigating the amount of HPV DNA in sequential skin biopsies during treatment with IQ 5%. A patient who had clinically 75% wart clearance at the end of study was found to have an 85% reduction of viral load in the lesion. This further supported the effectiveness of IQ in reducing HPV infection.

In conclusion, imiquimod, though its response is slow in comparing with destructive therapy, is an effective treatment in AGW. It also carries the following advantages. Patients need fewer office visits and therefore less time consuming. It is less painful and probably has fewer recurrences when comparing with other forms of treatments. Self-application can minimise embarrassment and also allow prompt treatment of new warts.

Learning points:

The goal of treatment of anogenital wart is removal of exophytic growth and amelioration of signs and symptoms but not eradication of HPV. Expensive therapies, toxic therapies and procedures that result in scarring, should be avoided (Recommendation of CDC).