Background

Genital human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the US. An estimated 20 million Americans are currently infected, with 6.2 million new cases occurring each year in people 14-44 years of age. Seventy-four percent of new cases occur in persons aged 15-24 years, and it is suggested >80% of sexually active women will acquire genital HPV by age 50. The majority of infections are asymptomatic and self-limited; however, persistent HPV infection with an oncogenic type can cause cervical cancer. HPV infection is also common among men. Approximately 1 million American men have genital warts caused by HPV, with 2 of every 1,000 men newly diagnosed.

More than 130 HPV types have been identified, with greater than 40 causing genital infection. Genital HPV is divided into two groups based on potential to cause cancer: high-risk or oncogenic types and low-risk or nononcogenic types. High-risk types (such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, and 73) can cause low-grade and high-grade cervical cell abnormalities as well as anogenital carcinoma. Together HPV-16 and 18 account for about 70% of cervical cancers. Low-risk types (mainly 6 and 11) cause most (90%) of the genital warts in males and females, recurrent respiratory papillomatosis, and nasopharyngeal papillomas, as well as low-grade disease of the cervix in women.

HPV Vaccines

Two HPV vaccines are currently available in the US, quadrivalent (Gardasil®) and bivalent (Cervarix®) vaccines. The Food and Drug Administration (FDA) approved the quadrivalent vaccine in 2006 and bivalent vaccine in 2009.

The quadrivalent vaccine is composed of four HPV type-specific virus-like particles (VLPs) prepared from the capsid protein of HPV-6, 11, 16, and 18 combined with aluminum adjuvant. This vaccine is recommended for females 9-26 years (in Canada the approved indication includes girls and women 9-45 years of age) and is administered intramuscularly according to a 3-dose schedule at 0, 2, and 6 months. The bivalent vaccine is composed of two VLPs of HPV-16 and 18 and is recommended for females 10-25 years through intramuscular injection according to a 3-dose schedule at 0, 1, and 6 months.

The efficacy of quadrivalent vaccine is well established. In a per-protocol analysis (two Phase III trials), vaccine efficacy was 100% (95% CI, 80.9-100) for prevention of HPV-16 or 18 related cervical intraepithelial neoplasia (CIN) grades 2/3. In Protocol 013, which included 5,442 females aged 16-23 years, vaccine efficacy was 100% (95% CI, 89.5-100) for prevention of any grade CIN related to the vaccine types. The three studies (Protocol 007, 013, and 015) demonstrated vaccine efficacy of 98.9% (95% CI, 93.7-100) for prevention of HPV-6, 11, 16, and 18 related genital warts and 100% (95% CI, 55.5-100) for prevention of HPV-16 or
The efficacy of bivalent vaccine is also well established. In a Phase III trial, which included 18,644 females aged 15-25 years, per-protocol cohort vaccine efficacy was 98.1% (96.1% CI, 88.4-100) for prevention of HPV-16 or 18 related CIN 2/3.

New Indications

Although < 25% of all HPV-related cancers occur in men, specific groups, such as men who have sex with men, have significantly higher rates of HPV-related diseases, including anal cancer. HPV-16 and 18 cause approximately 90% of anal cancers. Around 340,000 new cases of genital warts are reported in the US each year. In 2009, the FDA approved the quadrivalent vaccine for prevention of genital warts in young men. The Advisory Committee on Immunization Practices (ACIP) recommended permissive use but not routine use of the vaccine for males aged 9-26 years. More recently, regulatory approval was expanded in the US for prevention of anal cancer.

Recent data has demonstrated the quadrivalent vaccine to be effective in preventing anal intraepithelial neoplasia in males. A randomized, placebo-controlled, double-blind study conducted by Giuliano et al. included 4,065 males aged 16-26 years from 71 sites throughout 18 countries. Of these participants, 3,463 were heterosexual. At screening, subjects who had clinically detectable anogenital warts or genital lesions suggestive of existing HPV infection were excluded from the study. The participants were followed for 2.9 years.

Guiliano's study showed prophylactic administration of quadrivalent vaccine to be efficacious in the prevention of genital lesions associated with HPV-6, 11, 16, and 18 in males aged 16-26 years. In the intention-to-treat population, vaccine efficacy was 65.5% (95% CI, 45.8-78.6) for prevention of vaccine type lesions and 60.2% (95% CI, 40.8-73.8) for prevention of any external genital lesion regardless of HPV type. When the per-protocol population was analyzed, vaccine efficacy for prevention of external genital lesions related to HPV-6, 11, 16, and 18 was 90.4% (95% CI, 69.2-98.1) and the efficacy against condyloma acuminata was 89.4% (95% CI, 65.5-97.9). No cases of PIN (penile, perianal, or perineal intraepithelial neoplasia) lesions were observed in the per-protocol vaccine group, however, this finding was not statistically significant in the study. Limitations of the study include the narrow age-range of the subjects and the relatively short follow-up period. Additionally, subjects had no more than five lifetime sexual partners, which could result in overrepresentation of subjects with a low likelihood of HPV exposure at baseline and subsequent exposure.

Controversies

Several questions have arisen concerning the use of HPV vaccine in females, which have further expanded with approval of the vaccine for males.

Will the vaccine prevent not only genital lesions, but also cervical and anal cancer and ultimately death?

An answer to this question will likely depend on decades of observation. However, benefits of the quadrivalent and bivalent vaccines have been consistently reported. HPV vaccine also has other early benefits. As reported in end-of-study data from Phase IIB and Phase III (FUTURE I and II) trials, vaccination in the negative to 14 HPV types population reduced the proportion of women who experienced a cervical therapy by 42% (95% CI, 28-54), which may reduce adverse pregnancy outcomes related to these procedures. HPV vaccine may also reduce the number of preterm deliveries due to cervical therapies.

The probability of infection with HPV-6, 11, 16, and 18 in young women pre-sexual debut is very low, however, almost all women will come into contact with at least one type with only 0-4 sexual partners, thus, almost all young women may benefit from the vaccine. Studies have also shown that in women with evidence of current infection with at least one HPV vaccine type, quadrivalent vaccine may prevent disease caused by the remaining nonexposed vaccine types. Further, in women with cleared infections by an HPV vaccine type, quadrivalent vaccine has been shown to prevent recurrent disease caused by the same type.

Australia is the first country to mount a fully funded HPV immunization program for all females 12-26 years of age. Within the first two years the country witnessed a 59% (95% CI, 54-61) reduction in genital warts in this age group of females, with the proportion of women diagnosed declining from 11.7% to 4.8%. In heterosexual males aged 12-26 years, a 39% (95% CI, 33-46) reduction in men diagnosed with genital warts from 17.3% to 10.5% was observed within the same two-year period. This finding in men is suggestive of herd immunity attributable to reduced exposure to HPV in vaccinated women.

How long will protection conferred by the vaccine last?

Antibody titers reach their peak after the third dose, then decline gradually until month 24 and remain higher than those naturally infected. Phase IIB trials showed complete protection for the monovalent HPV-16 vaccine after 9.5 years, 6.4 years for the bivalent vaccine, and 4 years for the quadrivalent vaccine. HPV vaccine follow-up continues, with recent data indicating a rapid and strong anamnestic response induced by a fourth dose of HPV vaccine 6.8 years after the initial 3-dose vaccination course; all subjects demonstrated an approximate eight-fold increase in HPV-16 and 18 antibody titers 7 days after the fourth dose and a >16-fold increase after 1 month.

Since most HPV infections are easily cleared by the immune system, how will vaccination affect natural immunity against HPV, and with what implications?

Although most HPV infections are easily cleared by the immune system, interim lesions represent a substantial burden on the health care system and can cause psychosexual distress in patients. As well, persistent infections have significant implications as a cause of cervical cancer. Antibody response to HPV, in general, is specific for the HPV type; however, cross-reactivity has been noted. Recent studies suggest that the quadrivalent vaccine may also provide cross-protection against HPV strains not contained in the vaccine, but are closely related. Notwithstanding, the durability of immunity and the importance of these findings remain to be established.
**Will type replacement be seen?**

With the introduction of HPV vaccines, “type replacement” is a concern. Type replacement is a viral population dynamics phenomenon defined as elimination of some types causing an increase of others. It occurs when partial competition exists among different types during natural infection and the vaccine does not provide cross-protection against competing types. In HPV, natural competition does not appear to exist, therefore type replacement is unlikely.  

**How will the vaccine affect other oncogenic strains of HPV?**

There is risk of change in population dynamics for existing HPV types and viral mutations may occur to generate new variants that are equally oncogenic but not recognized by vaccine-induced antibodies. However, HPV uses host cell DNA polymerases, and thus, has a very slow mutation rate, suggesting this risk is very low.  

**How will vaccination affect screening practices?**

Cytological screening practices should not be modified since the endpoint of the vaccine (cervical cancer) may take decades before incidence change can be measured. It has been suggested by HPV vaccine biologic models that the vaccine may increase the screening intervals. Positive predictive value will drop, making viral testing more appealing.

**Other Vaccine Benefits**

All HPV lesions, including genital warts, are associated with significant physical and psychological morbidity, high treatment failure and recurrence rates, as well as substantial cost. The incidence of HPV infection is similar among both males and females, however, prevalence of infections is higher in males. Differences in immune response to HPV between genders have been described. A US study found HPV-seropositivity was higher in females than males (17.9% vs. 7.9%, respectively). The higher prevalence of HPV infections in men may be explained in part by the lower immune response to natural infection.  

The ACIP recommends routine vaccination of females aged 11-12 years (the vaccination series may be started as early as 9 years) and catch-up vaccination for females aged 13-26 years. Similarly, the European Centre for Disease Control and Prevention recommends that the primary target population for HPV vaccination should be young girls before they become sexually active, with catch-up vaccination administered in older girls and young women. These measures will likely accelerate the public health impact of vaccination while also increasing short-term benefits.

**Conclusion**

HPV vaccination represents an important approach in cancer-control strategies aimed at reducing the global incidence of cervical cancer. Routine vaccination of girls is already recommended and catch-up immunization programs have also been instituted for older girls not yet vaccinated in order to complete the schedule. The increasing prevalence of HPV-related cancers in males coupled with a lack of anal cancer screening underscores the importance of routine vaccination of boys, not only to benefit the boys themselves but also to reduce transmission to unvaccinated girls, thus further widening the impact of HPV vaccination.

**References**

Botulinum Toxin Type A: New Information about an Old Medicine
Kevin C. Smith, MD, FRCPC (Dermatology)
Private practice, Niagara Falls, ON, Canada

ABSTRACT
Now that several formulations of botulinum toxin type-A (BoNT-A) are on the market in North America and throughout the world, it is of great practical importance for those who administer these medications to be familiar with the differences between the formulations. These differences pertain to the stability of the medications, in particular during the period of time between reconstitution and administration, which may affect the degree of diffusion through various tissues after injection. A variety of relatively new uses of BoNT-A for dermatological conditions will be discussed.

Key words: botulinum toxin type-A, BoNT-A, abobotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, neuromodulator, BOTOX®, Dysport®, XEOMIN®

Medicines formulated from the highly purified, naturally occurring protein known as botulinum toxin type-A (BoNT-A) have been in use since 1980, when ophthalmologist Alan Scott used an injectable formulation of BoNT-A to treat strabismus and blepharospasm in humans. The first formulation of BoNT-A to become commercially available was onabotulinumtoxinA (BOTOX®), licensed in the United States in 1989 for treatment of three conditions: strabismus, blepharospasm, and hemifacial spasm. In recent years, two other formulations of BoNT-A have been licensed for use in the United States and a number of other countries: abobotulinumtoxinA (Dysport®) and incobotulinumtoxinA (XEOMIN®).

Those interested in BoNT-A should become familiar with the non-proprietary names for the various formulations of BoNT-A, because increasingly, presentations at meetings and in scientific publications are using the non-proprietary rather than the trade names for these products. A different non-proprietary name was assigned to each formulation of BoNT-A to reflect the fact that while the active ingredient in all three formulations is BoNT-A, the biological activity, in particular the stability and diffusion kinetics, of the active ingredient is modulated by the other components of the formulation, notably the protective proteins (hemagglutinins and non-hemagglutinins, which are associated with BoNT-A in onabotulinumtoxinA and abobotulinumtoxinA) and the amount and type of human serum albumin (added to the formulations to keep the BoNT-A in solution after reconstitution). Biological activity is also affected by the manufacturing process (as each BoNT-A formulation is manufactured differently), as well as other excipients in the vial (e.g., sodium chloride and sucrose). The effects (if any) on stability after reconstitution caused by the presence of trypsin-like proteolytic activity in incobotulinumtoxinA remain to be elucidated.

Non-interchangeability of Products
There is no consensus on how to switch patients between the three formulations. Each formulation is dosed using units specific to the product, which are determined in a manner that is proprietary to the manufacturer. It is important to note that because the dosing units are unique to each formulation, the products are considered to be non-interchangeable.

While it is possible to construct test systems in which various dose ratios can be compared under standard conditions (e.g., hyperhidrosis on the forehead or frontalis muscle contractions), there is no simple ratio that can be used to facilitate conversion of patients from one formulation of BoNT-A to another.

Widening Applications
Since Alan Scott’s pioneering use of BoNT-A for the treatment of blepharospasm and strabismus, various formulations of this versatile biological product have been reported to be useful in the management of over 140 medical, surgical, and aesthetic indications. Of interest to dermatologists, indications that regulatory authorities have approved for marketing and advertising in Canada include (for onabotulinumtoxinA) treatment of upper facial rhytides, including forehead, lateral canthus and glabellar lines, as well as for the treatment of hyperhidrosis of the axillae in patients 18 years of age and older. It is expected that other formulations of BoNT-A could receive similar regulatory approval for marketing and advertising in Canada in the future.

When they were first introduced, medicines incorporating BoNT-A were used to block the vesicle-mediated release of the neurotransmitter acetylcholine, and so produce for a period of several months very precise and localized relaxation of the striated muscles to which it was applied by injection. The first suggestion that BoNT-A could be used for purposes other than muscle relaxation came from Bushara and Park in 1994, who observed reduced sweating in the treated area when BoNT-A was used for treatment of hemifacial spasm. Based on observations that BoNT-A was useful for controlling excessive sweating, it was found to also be beneficial for the control of persistent facial flushing, gustatory sweating (Frey’s
Basic science research has shown that BoNT-A blocks the vesicle-mediated release of neurotransmitters other than acetylcholine, including substance-P, glutatione, and calcitonin-gene related peptide. These properties of BoNT-A may account for its neuromodulating effect on autonomic nerves, which makes possible the use of BoNT-A as a therapeutic option for Raynaud’s phenomenon, where treatment with BoNT-A can be safer and simpler than sympathectomy. Onset of action occurs within days and lasts for months, controlling rest pain, shortening and reducing the severity and frequency of attacks, and speeding the healing of ischemic ulceraions.

The observation that BoNT-A inhibits the release of some pain-mediating neurotransmitters, such as substance-P, helps to explain why BoNT-A has proven useful in the management of a variety of painful conditions, including headache, multiple cutaneous piloleiomomas, notalgia paresthetica, and post-herpetic neuralgia in the trigeminal distribution, but not on the trunk or extremities. BoNT-A has even proven to be of value in athletes, for example as a treatment for an intention tremor known as “the yips,” afflicting up to 30% of golfers. Similar dystonias and occupational cramps that can occasionally trouble dermatologic surgeons might also benefit from treatment with BoNT-A.

Systems for the topical administration of BoNT-A are in development, and may turn out to be useful for certain medical and aesthetic indications. The N-terminal light chain component of BoNT-A (known as LC) is the part that cleaves SNAP-25, resulting in the blockade of vesicle-mediated release of a variety of neurotransmitters. This component (or the corresponding LC element from other botulinum neurotoxins) can be attached to a variety of ligands, which are proteins that bind to various glycoproteins that are specific for certain cell types or can be produced by recombinant techniques.

It is likely that such derivatives of BoNT-A and other clostridial neurotoxins, which are now emerging from the labs and in some cases entering clinical trials, will become commercially available. These advances are poised to extend the utility of this class of medications to tissues that are currently unresponsive to BoNT-A, improve tissue specificity, modulate durations of action, and benefit our patients in ways that remain to be explored.

Conclusion

Medications formulated with BoNT-A as their active ingredient have a long record of safety and efficacy for a very wide and growing spectrum of medical and aesthetic indications. Future medications based on derivatives of BoNT-A are likely to further expand the range of utility and improve the risk/benefit ratio of this class of agents.

It is important for those interested in BoNT-A to become familiar with the non-proprietary names for the various formulations of BoNT-A, because non-proprietary nomenclature is being used exclusively in a growing number of academic and educational settings. Additionally, the use of non-proprietary names have been mandated by the US FDA to differentiate between the various formulations of BoNT-A.

It is important for those interested in BoNT-A to realize that each formulation of BoNT-A has unique pharmacologic and pharmacokinetic properties, and may behave differently in various clinical situations and indications, e.g., depending on the dosage, degree of dilution when the product is reconstituted, and the anatomic area being treated. For these reasons, there are no simple “universal” conversion ratios between the various formulations of BoNT-A.

References


20. Laing TA, Laing ME, O’Sullivan ST. Botulinum toxin for treatment of glau-


To get more information, medical professionals and consumers can access all of our sites from www.SkinInformation.com or go directly to:

### Patient sites:
- AcneGuide.ca
- DermatologyCare.ca
- HandEczema.ca
- MohsSurgery.ca
- SkinCancerGuide.ca
- UnwantedFacialHair.ca
- BotoxFacts.ca
- EczemaGuide.ca
- HerpesGuide.ca
- PsoriasisGuide.ca
- SkinCoverup.com
- CosmeticProcedureGuide.ca
- GenitalWarts.ca
- MildCleanser.ca
- RosaceaGuide.ca
- Sweating.ca
- StaphInfection.com

### Medical professional sites:
- Dermatologists.ca
- SkinTherapyLetter.ca
- PASItraining.com
- SkinCareGuide.ca
- SkinPharmacies.ca

### Social networking sites for patients and health care professionals:
- GenitalWartsPatients.com
- PsoriasisPatients.com

---

**Browse our archive of past issues**

We welcome your feedback.

Please email us with your comments and topic suggestions to: info@SkinTherapyLetter.com

---

**Indexed Edition**
for Dermatologists & Healthcare Professionals

[_skinTherapyLetter.com](http://www.SkinTherapyLetter.com)

**Family Practice Edition**

[SkinTherapyLetter.ca/fp](http://www.SkinTherapyLetter.ca/fp)

**Pharmacist Edition**

[www.SkinPharmacies.ca](http://www.SkinPharmacies.ca)
Skin Therapy Letter® (ISSN 1201-5989) Copyright 2011 by SkinCareGuide.com Ltd. Skin Therapy Letter® is published 10 times annually by SkinCareGuide.com Ltd. 1004 - 750 West Pender, Vancouver, British Columbia, Canada, V6C 2T8. All rights reserved. Reproduction in whole or in part by any process is strictly forbidden without prior consent of the publisher in writing. While every effort is made to see that no inaccurate or misleading data, opinion, or statement appears in the Skin Therapy Letter®, the Publishers and Editorial Board wish to make it clear that the appearance of moderate to severe nasolabial folds in adults. In clinical investigations, this autologous cell therapy demonstrated good tolerability and the most common reported adverse events were mild to moderate injection-site reactions that resolved within 1 week. The technological platform used to create this product is a patented process that extracts, isolates, and multiplies a person's own skin cells (collagen producing fibroblasts), which are then injected into the wrinkles.

The US FDA approved the first novel personalized aesthetic cell therapy in June 2011 for improving the appearance of moderate to severe nasolabial folds in adults. In clinical investigations, this autologous cell therapy demonstrated good tolerability and the most common reported adverse events were mild to moderate injection-site reactions that resolved within 1 week. The technological platform used to create this product is a patented process that extracts, isolates, and multiplies a person's own skin cells (collagen producing fibroblasts), which are then injected into the wrinkles.

The US FDA approved the first novel personalized aesthetic cell therapy in June 2011 for improving the appearance of moderate to severe nasolabial folds in adults. In clinical investigations, this autologous cell therapy demonstrated good tolerability and the most common reported adverse events were mild to moderate injection-site reactions that resolved within 1 week. The technological platform used to create this product is a patented process that extracts, isolates, and multiplies a person's own skin cells (collagen producing fibroblasts), which are then injected into the wrinkles.

The US FDA approved the first novel personalized aesthetic cell therapy in June 2011 for improving the appearance of moderate to severe nasolabial folds in adults. In clinical investigations, this autologous cell therapy demonstrated good tolerability and the most common reported adverse events were mild to moderate injection-site reactions that resolved within 1 week. The technological platform used to create this product is a patented process that extracts, isolates, and multiplies a person's own skin cells (collagen producing fibroblasts), which are then injected into the wrinkles.

The European Commission (EC) has granted marketing authorization to this new first-in-class human monoclonal antibody in July 2011 for the treatment of systemic lupus erythematosus (SLE). Treatment is indicated for adult patients with active, autoantibody-positive SLE who are receiving standard therapy.

The European Commission (EC) has granted marketing authorization to this new first-in-class human monoclonal antibody in July 2011 for the treatment of systemic lupus erythematosus (SLE). Treatment is indicated for adult patients with active, autoantibody-positive SLE who are receiving standard therapy.

5-fluorouracil cream 0.5% + Salicylic acid 10% Actikerall® Almirall, S.A.

The UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) granted marketing approval to this topical solution combination therapy in June 2011 for treating palpable and/or moderately thick hyperkeratotic actinic keratosis (grade 1/II) in adults. Good clinical efficacy was demonstrated in studies involving 168 patients, which confirmed histological clearance of lesions in 72% of patients and sustained clinical effect of 85.8% for lesions assessed as cleared after initial therapy and remained clear 12 months post-treatment.

In June 2011, the US FDA notified healthcare professionals that the Warnings and Precautions section of labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs has been revised to include new safety information about the increased risk of high-grade prostate cancer linked to the use of finasteride and dutasteride. This announcement follows the FDA's review of two large, randomized controlled trials - the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. Finasteride (Proscar®/Propecia®, Merck & Co.) and dutasteride (Avodart®/Jalyn™, GlaxoSmithKline) are used to treat male pattern hair loss and benign prostatic hyperplasia (BPH). Prior to initiating 5-ARI therapy, the FDA recommends physicians screen patients to rule out other urological conditions that can mimic BPH, including prostate cancer.

More information is available at: http://www.fda.gov/Drugs/DrugSafety/ucm258314.htm

In July 2011, the Japanese Ministry of Health, Labour and Welfare (MHLW) approved three products by Merck Sharp & Dohme Idea Inc. (MSD), an affiliate of Merck & Co.: 1. Gardasil® human papillomavirus quadrivalent (Types 6, 11, 16 and 18) recombinant vaccine is approved for the prevention of cervical cancer and their precursor lesions, vulvar and vaginal intraepithelial neoplasia grade 1/2/3, and genital warts caused by HPV types 6, 11, 16 and 18 in females ≥ 9 years of age.

2. Zolimza® (vorinostat) is an oral anticancer agent approved for treating cutaneous T-cell lymphomas.

3. Cubicin® (daptomycin for injection) is an antibiotic agent approved to treat methicillin-resistant Staphylococcus aureus (MRSA) infections.