• Treatment Options for Patients With Immune Thrombocytopenia
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• Increase in Bone Mineral Density During Testosterone Therapy in Chinese Hypogonadal Men
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• Clinical Evidence of the Quadrivalent HPV Vaccine in Adult Women Over 26
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Dermatology e-Alert

Welcome to the first issue of Dermatology e-Alert!
It is my pleasure to introduce the first edition of the HKASD Dermatology e-Alert. We hope that through this newsletter we can keep our colleagues in dermatology up to date with the latest topics, research, and events happening in Hong Kong and around the world.

Prof. Henry Hin Lee Chan MD, PhD (HK), FRCP (Lond), Edin, Glas, FHKCP, FHKAM (Med)
President, Hong Kong Association of Specialists in Dermatology

In This Issue
We focus on psoriasis and eczema and what can be done to alleviate these common conditions

**Emollient Tx From Birth May Prevent Eczema**
Beginning emollient therapy at birth is a safe and feasible approach to prevent eczema, results from a small pilot study suggest.
By: Doug Brun

**Fractional CO₂ Laser, Chemical Peel Compared**
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**Pavlovian Approach to Treating Psoriasis Proves Effective in Decreasing Dosages**
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**New findings in Acne Therapy**
Recent developments in the treatment of acne were discussed during a CME symposium by Prof. Diane M Triboutrot, Professor of Dermatology, The Pennsylvania State University College of Medicine, Hershey, PA, USA.
By: Prof. Diane M Triboutrot

**Atopic Eczema in Children**
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**Key Medical Papers**

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*J Am Acad Dermatol.* 2009 May;60(5 Suppl):S7-50

**Calcitriol ointment: a review of a topical vitamin D analog for psoriasis.**

**Reddish, scaly, and itchy: how proteases and their inhibitors contribute to inflammatory skin diseases.**

> MORE...
Editorial

In a world with rapid advances in medical research and technology, continuing medical education (CME) for doctors has been regarded as paramount. However, doctors practise in different environments. The two notable separate groups are those who work in public service and those working in the private sector, each with different needs for the kind of CME programme required.

Doctors in the public sector are luckier in this respect, as their CME activities are catered for in their hospital work schedules. Private doctors, on the other hand, need to attend meetings that are often in conflict with their work hours. Some doctors read our Journal, which contains good and practical information, but this does not help scoring for official CME schemes. We hope the assessors of these schemes will take into consideration the different work environments of doctors, and take an encouraging and compassionate attitude in helping doctors to fulfill their CME requirements.

Dr Lam Tat Chung, Paul
FRCP, FHKAM (Medicine), FHKAM (Psychiatry)
President

Dr Lau Chu Pak
FRCP, MD, FHKAM (Medicine)
Chief Editor

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Dr Lo Siu Fai, Leslie (盧兆輝醫生)
Immune thrombocytopenia (ITP) is an autoimmune disorder representing one of the many causes of thrombocytopenia. Chronic ITP is most often observed in adults and has a persistent course lasting for many years. It is characterized by recurrent relapses and frequently requires medical intervention.

According to the guidelines published by the American Society of Hematology in 1996,¹ the diagnosis of ITP is based primarily on the patient’s medical history, physical examination, complete blood count and peripheral smear, and should include the following:

- History compatible with the diagnosis of chronic ITP;
- Normal physical examination findings except for signs of thrombocytopenia (petechiae, purpura or mucosal bleeding), with no adenopathy or splenomegaly;
- Complete blood count showing isolated thrombocytopenia with large platelets, but no anaemia unless bleeding or immune haemolysis is present;
- Bone marrow examination showing normal or increased numbers of megakaryocytes (may not be required for diagnosis unless the manifestation is unusual or the patient is older than 60 years of age);
- No clinical or laboratory evidence for other causes of thrombocytopenia.

The British Committee for Standards in Haematology (BCSH) suggested that in adults without bleeding symptoms or adults with a platelet count >30,000 cells/µL, therapy is not indicated unless they are undergoing a procedure likely to cause blood loss, such as surgery, dental extraction or childbirth.²

**Conventional Treatment Options for Primary ITP**

ITP is now considered a disorder not only of increased platelet destruction, but also of diminished platelet production. This has led to the investigation of thrombopoietic growth factors as a treatment option. However, most currently available treatment options, such as corticosteroids, intravenous immunoglobulins (IVIgs), splenectomy, rituximab and immunosuppressive agents, are primarily aimed at reducing platelet destruction.

Corticosteroids such as prednisone are the standard first-line treatment for ITP. Minimal corticosteroid exposure is a tenet of therapy for chronic ITP.³ To avoid complications, prednisone should be rapidly tapered and usually stopped in responders and nonresponders after 4 weeks of treatment. Initial studies of single-agent prednisone in ITP demonstrated an impressive response to treatment in approximately 70% of patients. However, these responses were usually short-lived; at 1 year, platelet counts in the normal range were observed in only 5% to 15% of patients.⁴

Another steroid used more recently in ITP is high-dose dexamethasone. For optimal therapeutic effect, it appears that the agent must be given soon after diagnosis. Cheng and colleagues demonstrated that treatment with a single course of 4 days of pulse dexamethasone resulted in sustained response requiring no further treatment during >6 months of follow-up in 50% of patients.⁵ Subse-
sonized platelets. but appears to be interference with the of action of IVIg is not well understood, considered. The dominant mechanism and thromboembolic events, must be failure, headache, aseptic meningitis including allergic reactions, fever, renal levels within 3 to 4 weeks. Furthermore, the effect is often short-lived, with the platelet count returning to pretreatment levels within 3 to 4 weeks. Moreover, treatment-associated adverse effects, including allergic reactions, fever, renal failure, headache, aseptic meningitis and thromboembolic events, must be considered. The dominant mechanism of action of IVlg is not well understood, but appears to be interference with the Fcγ receptor–mediated clearance of opsonized platelets.

Anti-D immunoglobulin is also used in the treatment of ITP, but is only appropriate for RhD-positive, nonsplenectomized patients who do not have antibodies on their red blood cells. Anti-D immunoglobulin is enriched with antibodies directed to the RhD antigen on red blood cells. The agent is thought to act by blocking the mononuclear phagocytic system.

Both IVlg and anti-D immunoglobulin are recommended for the treatment of ITP in patients with critical bleeding or patients who are refractory to corticosteroid treatment. These agents typically result in a more rapid increase in platelet count than corticosteroids. (Table)

### Newer Treatment Options for Primary ITP

In 2008, two novel agents – romiplostim and eltrombopag – received US Food and Drug Administration approval for the treatment of chronic ITP in patients who had insufficient response to previous therapy with corticosteroids, immunoglobulins or splenectomy. In contrast to the other agents that prevent destruction of antibody-coated platelets, these thrombopoietin receptor agonists stimulate the production of platelets.

### Romiplostim

Romiplostim was approved based on the findings of two parallel, placebo-controlled phase III trials. In these trials, romiplostim treatment was associated with significantly increased platelet counts in both splenectomized and nonsplenectomized ITP patients. The approved initial dose of romiplostim is 1 µg/kg subcutaneously once weekly, with escalation to a maximum dose of 10 µg/kg permitted based on platelet response. Sustained response, defined as platelet counts ≥50,000 cells/µL for at least 6 of the last 8 weeks of the 24-week trial, was observed in 25 of 41 nonsplenectomized patients and 16 of 42 splenectomized, highly refractory patients. The overall response rate (any 4 out of 24 study weeks with platelet counts ≥50,000 cells/µL) was 88% and 78.6% in the non-splenectomized and splenectomized groups, respectively (vs 0% and 14% in the respective placebo arms).

The most significant adverse event observed in patients receiving long-term romiplostim is the development of reticulin fibrosis in the bone marrow. Long-term data with romiplostim showed that responses were sustained for up to 4 years on continuous therapy, with most patients being able to decrease or discontinue concurrent corticosteroid therapy.

### Eltrombopag

Eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist, was granted accelerated approval for the treatment of thrombocytopenia in patients with an insufficient response to corticosteroids, immunoglobulins or splenectomy based on results of two 6-week phase II and III studies. In the phase II study, 70% and 81% of patients receiving eltrombopag 50 mg and 75 mg per day, respectively, achieved a platelet count of 50,000 cells/µL by day 43 (vs only 11% of patients in the placebo arm). The 6-week results of the phase III Eltrombopag Extended Dosing Study (EXTEND) demonstrated that 59% of patients given eltrombopag 50 mg achieved platelet counts ≥50,000 cells/µL, compared with 16% of patients receiving placebo. In a continuation of this study, rechallenge with eltrombopag resulted in platelet counts increasing to

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Table. Time to first and peak platelet responses of individual agents for treatment of ITP

<table>
<thead>
<tr>
<th>Agent/treatment</th>
<th>Reported dose range</th>
<th>Time to initial response* (days)</th>
<th>Time to peak response* (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>1–4 mg/kg PO daily x 1–4 weeks</td>
<td>4–14</td>
<td>7–28</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg PO or IV daily x 4 days for 4–6 courses every 14–28 days</td>
<td>2–4</td>
<td>4–28</td>
</tr>
<tr>
<td>IVlg</td>
<td>0.4–1 g/kg per dose IV (1–5 doses)</td>
<td>1–3</td>
<td>2–7</td>
</tr>
<tr>
<td>Anti-D</td>
<td>75 µg/kg per dose IV</td>
<td>1–3</td>
<td>3–7</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² per dose IV (4 weekly doses)</td>
<td>7–56</td>
<td>14–180</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Laparoscopic</td>
<td>1–56</td>
<td>7–56</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Up to 2 mg/dose IV (4–6 weekly doses)</td>
<td>7–14</td>
<td>7–42</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>0.1 mg/kg per dose IV (6 weekly doses)</td>
<td>7–14</td>
<td>7–42</td>
</tr>
<tr>
<td>Danazol</td>
<td>400–800 mg PO daily</td>
<td>14–90</td>
<td>28–190</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 mg/kg PO daily</td>
<td>30–90</td>
<td>30–180</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>3–10 µg/kg/week SC</td>
<td>5–14</td>
<td>14–60</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>50–75 mg PO daily</td>
<td>7–28</td>
<td>14–90</td>
</tr>
</tbody>
</table>

* In the times to the initial and peak responses, the first number of days is the first time that a response could be reasonably expected and the second number of days is the time after which a response to this particular agent becomes less likely when administered at the dose and schedule listed in the table. Dosages, where not given on kilogram/body weight basis, are intended for adults.

Adapted from reference 3.
>50,000 cells/µL in more than 90% of the initial responders. Importantly, no differences in response rates were observed between patients who were refractory (ie, postsplenectomy) and those who failed to respond to classical treatment, which suggests that eltrombopag may be effective in both steroid-refractory and splenectomized patients. Saleh and colleagues recently presented updated results from the EXTEND trial, with ≥6 months of follow-up data in most patients (n=240/299) and 24 months of follow-up data in a few (n=17/299).14 Overall, the efficacy results were reassuring, with 86% of patients achieving a platelet count of ≥50 x 10^9/L and median platelet counts remaining at ≥50 x 10^9/L over time after week 2.

Two recently presented studies investigated the longer-term effects of eltrombopag treatment in patients with refractory ITP. Results from the phase III Randomized Placebo-controlled Idiopathic Thrombocytopenic Purpura Study with Eltrombopag (RAISE) showed that patients receiving eltrombopag were eight times more likely to achieve a platelet count of >50,000 cells/µL than those receiving placebo, and were significantly less likely to require rescue medications (18% vs 40% with placebo; p<0.001).15 Again, in this study there was no significant difference in response between patients who had undergone splenectomy and those who had not. Like romiplostim, eltrombopag appears to increase reticulin fibrosis. In addition, some patients developed elevated liver enzymes, although treatment discontinuation was not required in most cases.

Conclusions and Recommendations

The diagnosis of ITP cannot be confirmed with any single test. This is further complicated by the numerous causes of thrombocytopenia unrelated to ITP. The most suggestive finding that “confirms” the diagnosis of ITP is a substantial response to an ITP-specific therapy (eg, IVlg).

Until recently, the standard of care for ITP had been corticosteroids or splenectomy. Management of the condition has changed significantly since 2008 as the thromopoietin receptor agonists, romiplostim and eltrombopag, became available. Several clinical trials are under way to assess these agents and other treatments for ITP.

With the availability of newer agents, the standard treatment for ITP has become less clear. Treatment must be tailored more to patient and disease characteristics, weighing the risks and benefits.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org
A 41-year-old male working as an electronic equipment technician presented with a history of repeated falls for 3–4 months. This usually occurred during the day as he walked to various parts of the office. The falls came without any warning so that the patient was not able to prevent them. He would hit the ground, causing bruises to his body and limbs. There was no loss of consciousness, convulsion, jerks, tongue biting, incontinence, confusion or motor weakness after the falls. The patient would get up and carry on with his work afterwards. He had 2–3 falls per week.

He also reported visual hallucination of small children following him around in the morning as he was preparing to go to work. His wife reported that he frequently got up at night to stand by and stare at the window soon after he fell asleep. The patient had no recollection of such episodes. Otherwise the patient had good health. He had mild anxiety due to work pressure.

Questions:
1. What is the likely diagnosis?
2. What tests need to be done?
3. What is the treatment?

Please turn to page 36 for discussion.

References:
2. Elyman LH et al. Supportive Care in Cancer 2007 15 (11): 1293-300
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CardioMetabolic Care
Sixty percent of osteoporosis cases in male patients are due to secondary causes. Hypogonadism, glucocorticoid excess and alcoholism constitute three major causes of male osteoporosis.

Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis. Abnormalities of the HPG axis at the testicular level cause primary testicular failure, while central defects of the hypothalamus or pituitary cause secondary testicular failure. Primary testicular failure results in low testosterone level, impairment of spermatogenesis and elevated gonadotropin levels. Secondary testicular failure is associated with low or low-normal gonadotropin levels, and low testosterone levels.

**Table 1. Symptoms suggestive of androgen deficiency in male**

**Specific symptoms:**
- Incomplete sexual development
- Eunuchoidism (arm span > height)
- Azospermia
- Reduced libido
- Decreased spontaneous erection
- Gynaecomastia
- Loss of body hair, reduced shaving
- Small testes
- Inability to father children
- Height loss, low-trauma fracture, low bone mineral density
- Reduced muscle bulk and strength
- Hot flushes, sweats

**Nonspecific symptoms:**
- Decreased energy, motivation, aggressiveness
- Depressed mood
- Poor memory and concentration
- Sleep disturbance
- Mild anaemia
- Increased body fat

Sixty percent of osteoporosis cases in male patients are due to secondary causes”

Serum testosterone level should be measured in patients with symptoms and signs listed in Table 1. Serum total testosterone concentrations, representing the sum of unbound and protein-bound testosterone in circulation, are measured by radioimmune assay or immunometric assay. Most of the circulating testosterone is bound to sex hormone-binding globulin (SHBG) and to albumin. Only 0.5% to 3% of circulating testosterone is unbound or free. Bioavailable testosterone refers to unbound testosterone plus testosterone loosely bound to albumin. Total testosterone levels are affected by alteration in SHBG that occurs in obese men, the elderly, men with comorbid diseases, hyper- or hypothyroidism, acromegaly, and men taking certain medications,
The clinical presentation of male hypogonadism depends on the age of onset of androgen deficiency. Onset in adulthood differs from prepubertal onset in clinical presentation.

Testosterone Therapy for Male Hypogonadism

Testosterone therapy has been shown to increase spinal bone mineral density (BMD) by 5.1% and trabecular bone mass by 14.3% over 18 months in 36 patients with acquired hypogonadism. Snyder et al showed that transdermal testosterone therapy increased BMD of the spine by 7.7% and that of the hip by 4.0% over 36 months in 18 hypogonadal men.

The author has reviewed BMD data in 31 hypogonadal men aged 25 to 68 years. They were put on intramuscular injection of mixed testosterone esters every 3 weeks. Twenty-one patients were diagnosed to have secondary hypogonadism (pituitary chromophobe adenoma: 10; idiopathic hypogonadism: 4; craniopharyngioma: 2; empty sella syndrome: 2; Kallmann’s syndrome: 2; idiopathic hypogonadotrophic hypogonadism: 1). Ten patients had primary hypogonadism (Klinefelter’s syndrome: 8; previous testicular damage: 2). Eleven patients had prepubertal onset of hypogonadism, while 20 patients had acquired hypogonadism in adulthood. All patients were hypogonadal as evidenced by a mean pretreatment testosterone level of 0.76 nmol/L. Androgen replacement normalized the testosterone level to 13.8 nmol/L. Those with secondary hypogonadism had statistically significantly lower testosterone level than those with primary hypogonadism. In addition, 19.4% of the patients suffered from fractures. One patient even suffered from five vertebral fractures. There was no significant difference between the baseline BMD of patients with primary vs secondary hypogonadism, and in patients with prepubertal vs postpubertal hypogonadism. There was a strong inverse association between the initial BMD and the annual rate of increase in BMD during testosterone therapy. (Figure)

“"The single most important determinant of the initial rate of increase in BMD during testosterone therapy is the baseline BMD""

In conclusion, regular intramuscular injection of mixed testosterone esters significantly increases BMD in Chinese hypogonadal men. The rate of increase in BMD is highest in the first 2 years of treatment, and in those with the lowest baseline BMD level. The response to treatment is regardless of the aetiological causes and the patient’s age. The single most important determinant of the initial rate of increase in BMD during testosterone therapy is the baseline BMD.

References:
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* The clinical significance of in vitro activity is unknown.
† TYGACIL does not cover Pseudomonas aeruginosa
* Infections caused by susceptible micro-organisms.

Reference: 1. TYGACIL® (tigecycline) prescribing information, Hong Kong (version 06/07).
Detail prescribing information available upon request.
The list of differential diagnoses for repeated falls include syncope, seizure, transient ischaemic attack, Ménière’s disease, posterior fossa tumour, colloid cyst of the third ventricle, normal pressure hydrocephalus and cerebellar syndromes. Other less likely considerations are peripheral neuropathy, motor neuron disease, cord compression syndrome and Parkinson’s disease, etc.

For syncope, we would expect more warning and accompanying signs such as palor, sweating, blurred vision, or light-headedness with or without postural onset. Seizure needs to be considered seriously. However, the attacks did not resemble tonic-clonic convulsions. Atonic seizures usually start in childhood. Nevertheless, EEG and brain scan should be recommended. For transient ischaemic attack, we would expect the patient to be older with risk factors for cerebral vascular disease. There were no supporting symptoms of motor weakness, visual field defects, aphasia, etc. Ménière’s disease was unlikely because the patient did not have complaints of vertigo, deafness or tinnitus.

The history of sleepwalking pointed to a sleep-related disorder. A sleep disorder with repeated falls would suggest cataplexy. The falls were consistent with attacks of cataplexy. Hallucination is an associated phenomenon. Although most texts cite hypnagogic hallucination, hypnopompic hallucination is also possible.

The classical narcoleptic tetrad described by Yoss and Daly consisted of excessive daytime sleepiness (100%), cataplexy (70%), hypnagogic hallucinations (30%) and sleep paralysis (25%). However, cataplexy is the central pathology of the syndrome. It is due to sudden intrusion of rapid eye movement (REM) sleep in the waking state, resulting in loss of muscle tone and uncontrollable falling. The atypical feature in this case is the absence of narcolepsy, which makes the case a very rare presentation.

The suggested test is multiple sleep latency test, in which the patient is put in a sleep laboratory overnight, and should have normal sleep. During the next day, the patient is asked to try to go to sleep every 2 hours, and is waken up once he falls asleep. The sleep latency is measured. Normal individuals fall asleep in 10–15 minutes. For those with excessive daytime sleepiness, the sleep latency is 2–5 minutes. Moreover, for those with cataplexy syndrome, REM sleep may emerge 10–15 minutes after sleep onset. This serves to confirm the diagnosis. Lumber puncture may reveal a low level of orexin 1 (hypocretin 1) of less than 100 pg/mL in the cerebrospinal fluid.

The patient responded dramatically well to REM-suppressing drugs, ie, sertraline 50 mg in the morning and trimipramine 50 mg nocte. He slept well with no more sleepwalking with a low dose of benzodiazepine hypnotic.
Clinical Evidence of the Quadrivalent HPV Vaccine in Adult Women over 26

Worldwide, cervical cancer is the fifth most deadly cancer in women. In Hong Kong, it is the seventh most prevalent and the eighth most deadly cancer in women, with 399 new cases and 129 deaths registered in 2007.

Human Papillomavirus (HPV) infection is known to be the major cause of cervical cancer. Among the diversity of over 100 types of HPV, HPV 6, 11, 16, and 18 are the most common types causing the majority of HPV-related diseases. HPV 16 and 18 are known to account for 70% of cervical cancer cases, and HPV 6 and 11 are associated with 90% of the genital warts, and around 10% of the mild Cervical Intraepithelial Neoplasia (CINI) cases.

Findings of Quadrivalent HPV vaccine in young women (Age 16-26)

Currently, the prophylactic quadrivalent HPV vaccine (namely Gardasil) is available to protect women from infection by HPV 6, 11, 16, and 18. Efficacy of the vaccine for women aged 16 to 26 years has been proven clinically. Such vaccine has now become the most effective way to prevent genital warts, vulvar, vaginal and cervical cancers, and has been shown to be up to 100% effective in preventing vaccine type related diseases.

Since HPV is mainly transmitted through sexual contact, early vaccination before a female becomes sexually active is recommended. Although the peak incidence of HPV infection occurs shortly after first sexual experience in most populations, all women remain at risk for acquisition of HPV infections. A recent study was conducted to assess the vaccine's efficacy, safety, and immunogenicity for adult women aged 24 to 45 years.

Study Design of Adult Women Study (Age 24-45)

3,819 women aged 24 to 45 years with no history of genital warts or cervical diseases were enrolled from community and academic health centres and primary health-care providers. The study was conducted in a multicentre, parallel, randomized, placebo-controlled, double-blind, and randomized setting. Participants were allocated to receive quadrivalent HPV vaccine (n=1,911) or placebo (n=1,908) by computer-generated randomization at day 1 and month 2 and month 6. All participants, study site investigators and personnel, study monitors, and central laboratory personnel were blinded to treatment allocation.

Covariantly, efficacy endpoints, which are the main efficacy outcome measures, included 6 months or more duration of infection and cervical and external genital disease due to HPV 6, 11, 16, 18 (first covariant endpoint) and due to HPV 16 and 18 alone (second covariant endpoint). The secondary efficacy endpoint was the combined incidence of infection related to HPV 6 or HPV 11 of 6 months or more duration, and cervical and external genital disease including genital warts.

Primary efficacy analyses were done in a per-protocol population. In the per-protocol population, all participants were tested negative for the relevant vaccine HPV type on day 1 and up to month 7. These women also had all 3 vaccine doses within 1 year and had at least one follow-up visit after month 7.

HPV infection rate in Adult Women Study

Nearly 100% recruited women were sexually active and over 80% had pregnancy history. Notably, about 90% of the subjects enrolled were naïve to 3 or 4 vaccine types. About a third of the subjects (33.2%) were positive to HPV 6, 11, 16, or 18 at baseline by serological or DNA testing, and additionally, most of the subjects positive to vaccine-type HPV were positive to only one HPV type. Only 0.4% was infected with all 4 vaccine types. That means the quadrivalent HPV vaccine could still potentially benefit these women via protection against vaccine HPV types which they are not infected with.
Proven Efficacy of Quadrivalent HPV vaccine in Adult Women Study (Age 24-45)

During the study, a total of 1,910 women received at least one dose of vaccine and 1,907 received at least one dose of placebo. No serious vaccine-related adverse events were reported.

In the per-protocol population, efficacy against the first cervical endpoint was 90.5%. Among 4 cases reported in vaccine arm, 3 HPV 16 related infections could be missed HPV positive cases and represent latent or early infections at baseline. Only one HPV 16 related CIN 2 was reported, which was likely caused by HPV51 at enrollment. HPV 16 has not been detected in the CIN 2 biopsy. These data are summarized in Table 1.

Table 1: Efficacy against the combined incidence of vaccine-type-related infection of at least 6 months' duration and CINs

<table>
<thead>
<tr>
<th>Vaccine (n = 1,910)</th>
<th>Placebo (n = 1,907)</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6/11/16/18-related (first cervical endpoint)</td>
<td>1,515</td>
<td>4</td>
</tr>
</tbody>
</table>

Rate = Incidence rate per 100 person-years at risk.

These results suggest that the quadrivalent HPV vaccine is highly efficacious in women aged 24 to 45 years who are not infected with the relevant HPV types at enrollment.

Quadrivalent HPV vaccine prevents re-infection and re-activation of disease

A subset of Phase III study subjects (n = 2,617) were HPV seropositive and DNA negative at enrollment for ≥1 vaccine type. These women indicated evidence of previous infections with vaccine types, but did not carry the virus at baseline. In each study, subjects were randomized in a 1:1 ratio to receive vaccine or placebo at day 1, month 2 and month 6 (without knowledge of baseline HPV status). Procedures were performed for efficacy data evaluation for an average of 40 months. No subject receiving HPV8/11/16/18 vaccine developed disease to a vaccine HPV type to which they were seropositive and DNA negative at enrollment. 7 subjects in the placebo group developed cervical diseases. The prevention efficacy was 100% (95% CI: 28.7-100.0).

These results suggest that antibodies elicited by natural infection may not provide complete protection from subsequent HPV re-infection / reactivation and related disease over time, and that the robust immune response to the quadrivalent HPV vaccine may prevent recurrence or reactivation of disease with vaccine HPV types.

Impact of the Quadrivalent HPV vaccine in women who have undergone definitive therapy

In the combined trials of phase III studies, 587 vaccine recipients and 763 placebo recipients underwent conventional definitive therapy. The average post-therapy follow-up was 1.5 to 1.6 years. Vaccine efficacy for any subject who developed CIN1 following surgery was 47% (95% CI: 17-66). In protocol 013, 222 vaccine recipients and 306 placebo recipients were treated for VIN1-3, VaIN1-3 or GWs. The average post-therapy follow-up was 1.5 to 1.9 years. Vaccine efficacy for these endpoints post-therapy was 44% (95% CI: 14-64). Efficacy for endpoints associated with HPV 6/11/16/18 was 74% for CIN (95% CI: <0, 97) and 79% for VIN1-3, VaIN1-3 or GWs (95% CI: 53-82). The vaccine efficacy will not be expected to be 100% as shown in per protocol populations in the studies. Nevertheless, women who have been treated previously for CIN, VIN, VaIN, or Genital Warts benefit from receiving quadrivalent HPV vaccine.

Who should be vaccinated?

The first efficacy study testing quadrivalent HPV vaccine in women over 26 has suggested high vaccine efficacy comparable to younger women. This vaccine has also been demonstrated to prevent reinfections or reactivation of diseases with previously infected HPV types. In addition, even women who have been treated for HPV related diseases may benefit from the vaccination.

These clinical data concluded that quadrivalent HPV vaccine is proven to be efficacious and safe in women over 26. However, regular pap screening is highly recommended for all women who are sexually active irrespective of vaccine status.

References:
2. Hong Kong Cancer Registry, Hospital Authority. Available at: http://www.ha.org.hk/cancerreg_cancerreport.html
Clinical data in women aged 24 - 45 was first published in the LANCET and is now included in product circular of GARDASIL®.

Help reduce the burden of the following diseases:

- Cervical Cancer
- Vulvar Cancer
- Vaginal Cancer
- Genital Warts

caused by HPV 6, 11, 16, 18

* See Clinical data (efficacy and safety) in Product Circular Section XII. CLINICAL PHARMACOLOGY and XV. SIDE EFFECTS

Selected Safety Information:
GARDASIL® (Quadrivalent HPV [Types 6, 11, 16, 18] Recombinant Vaccine) is indicated in 9-26 years old girls and women for the prevention of cervical, vulvar, and vaginal cancers; precancerous or dysplastic lesions and genital warts caused by HPV Types 6, 11, 16 and 18. It should be administered intramuscularly as 3 separate doses at 0, 2nd, 6th month. It is contraindicated in individuals with hypersensitivity to any vaccine ingredients or after a previous dose of GARDASIL and is not recommended for pregnant women. Pregnancy should be avoided during the vaccination period. This vaccine will not protect against diseases that are not caused by HPV and is not intended to be used for treatment of active genital warts, cervical, vulvar, or vaginal cancers; CIN, VIN, or VaIN. Routine cervical screening should be continued. Common adverse reaction in clinical trials were fever, injection-site pain, swelling, erythema, pruritus & bruising which were mild to moderate. Post-marketing reports: dizziness, headache, syncope, nausea & vomiting. Before prescribing, please consult the full prescribing information.

References:

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Treatment Options for Patients With Immune Thrombocytopenia

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References


