

Imiquimod: a new immunomodulatory drug

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Imiquimod a recently developed imidazoquinolin heterocyclic amine belongs to a new class of drug, immune response modifier agents, which can be attributed to the induction of a number of cytokines including interferon-alpha (IFN-alpha), interferon-gamma (IFN-gamma), tumor necrosis factor-alpha, interleukins-1, -6, -8, -12. Imiquimod increases in interferon and tumor necrosis factor in cultures of cells isolated from animal skin, and increases interleukin-8 concentrations in human keratinocyte and fibroblast cultures. Although in vitro studies have shown that imiquimod has no direct antiviral effects, the drug does exhibit antiviral and antitumor effects in vivo through induction of human cytokines. Although imiquimod cream recently became available for the treatment of genital and perianal warts, the topical mechanism of action of imiquimod is not yet fully understood. It is believed that stimulation of local cytokines by imiquimod leads to a reduction in human papilloma virus (HPV) load; to wart regression and to the normalization of keratinocyte proliferation without evidence of scarring. Treatment with topical 5 % imiquimod cream has shown promising results in the treatment of genital warts in immunocompetent individuals. Furthermore, it is an interesting alternative therapeutic method for other cutaneous viral skin lesions among immunocompetent and HIV-infected patients.

Keyword : *Imiquimod.*

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Objective : To introduce a new drug, imiquimod, to the reader.

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วารสาร วชิรเวช. อิมิควิโมด ยาชนิดใหม่ กลุ่มออกฤทธิ์ผ่านกลไกทางภูมิคุ้มกัน. จุฬาลงกรณ์-
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Imiquimod เป็นยาชนิดใหม่ ในกลุ่มที่ออกฤทธิ์ผ่านกลไกทางภูมิคุ้มกันเป็นสารประกอบในกลุ่ม *imidazoquinolin heterocyclic amine* ที่สามารถชักนำก่อให้เกิด *cytokine* ได้หลายชนิดเช่น *interferon-alpha (IFN-alpha)*, *interferon-gamma (IFN-gamma)*, *tumor necrosis factor-alpha*, *interleukins-1, 6, 8* และ *12* *imiquimod* เพิ่ม *interferon* และ *tumor necrosis factor* ใน *cell culture* ของผิวหนังสัตว์ทดลองและเพิ่ม *interleukin-8* ใน *keratinocyte* และ *fibroblast* ของมนุษย์ ถึงแม้ว่าการศึกษาในหลอดทดลองจะไม่พบผลต่อต้านไวรัสโดยตรงของ *imiquimod* แต่พบผลการต่อต้านไวรัสและเซลล์มะเร็งทางอ้อมผ่านกลไกการชักนำ *cytokines* ดังได้กล่าวมาแล้ว *imiquimod* ในรูปครีมนั้นได้ถูกนำมาใช้อย่างแพร่หลายในการรักษาหูดที่อวัยวะเพศ ทั้งนี้กลไกการออกฤทธิ์ที่แท้จริงของยานี้ยังไม่เป็นที่ทราบอย่างแน่ชัด แต่เชื่อว่าความสามารถชักนำให้เกิด *cytokine* ของยานี้ทำให้เกิดการลดลงของ *human papilloma virus (HPV)* นอกจากนี้ยังพบว่าการใช้ยานี้ในการรักษาโรคผิวหนังที่เกิดจากไวรัสอีกหลายชนิดของทั้งผู้ป่วยที่มีภูมิคุ้มกันปกติและผู้ป่วยที่เป็นโรคภูมิคุ้มกันบกพร่องให้ผลการรักษาที่ดี

คำสำคัญ : *Imiquimod*

Imiquimod is a new pharmaceutical product recently presented to physicians. Imiquimod, an imidazoquinoline amine, is a new immune response modifier agent recently approved for the topical treatment of external genital and perianal warts.⁽¹⁻¹⁰⁾ Compared with the other routine therapeutic options for genital and perianal warts, imiquimod is easier to use and can be self-administrated by patients. Imiquimod exhibits no direct antiviral or antiproliferative activity when tested in a number of cell culture systems. Its activity was discovered while screening for anti-herpes virus activity. One of the first analogs in the series, S -25059 was tested in the early 1980's and due to its slight toxicity, caused some reduction of herpes cytopathology in cell cultures.⁽¹⁻³⁾ The dosage form of this drug is cream, generally known as ALDARA.⁽⁵⁾ The chemical name of imiquimod is 1-(2-methylpropyl)-1 H-imidazol [4,5-c] quinolin - 4 - amine, with the molecular formula, $C_{14}H_{16}N_4$. The molecular weight of this substance is about 240.3. Its structure is shown in figure 1.

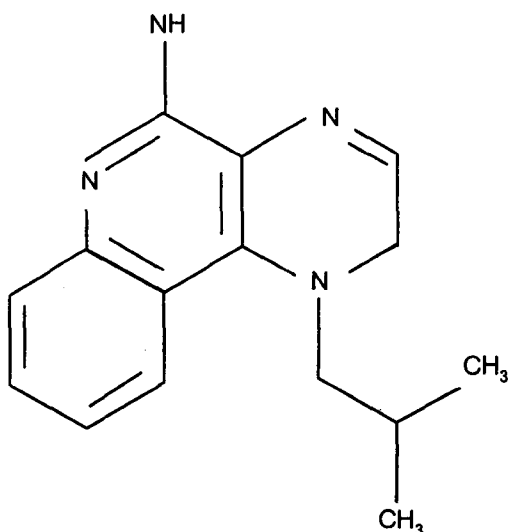


Figure 1. Structure of imiquimod.

General information about Imiquimod

Pharmacological information

1. Pharmaceutical property^(5,11)

The most common form of imiquimod is cream. Generally it is white to slightly yellow cream, packed in a single use foil sachet. Each sachet contains 250 mg of cream, which is enough to cover a wart area of 20 square centimeter. Routinely, 250 mg cream contains 12.5 mg of active ingredient, providing 5 % imiquimod cream. The cream base contains selected surfactants, preservatives, and viscosity-enhancing excipients to formulate an oil-in-water cream indicated that fatty acids were the preferred solvent for topical imiquimod formulations, and isostearic acid (ISA). A combination of polysorbate 60, sorbitan monostearate, and xanthan gum was used to produce a physically stable cream. The preservative system included parabens and benzyl alcohol to meet the USP criteria for preservative activity.⁽¹¹⁾ It has a pKa of 7.3, indicating a weak base. The 1 % and 2 % imiquimod cream is also produced but is not widely used. Furthermore, both 1 % and 2 % imiquimod are thermolabile; therefore, it should be kept at low temperature but not frozen. The oral form of imiquimod currently has limited use due to its known adverse effects.

2. Pharmacostatic property^(5,11)

Only a small amount of the active ingredient in the imiquimod cream is absorbed into the skin, and a smaller part absorbed into systemic circulation. Less than 0.9 % is excreted via urine and feces. Ingestion of the cream form of imiquimod is not recommended.

3. Pharmacodynamic property^(12 - 25)

Although the majority of immunomodulatory agents available or in development inhibits pathways involved in immune activation, imiquimod is unique in that it activates immune function.^(12 - 25) The exact mechanism of imiquimod's antiviral activity is unknown; however, its effects are likely to be related to its immunomodulating properties. Although *in vitro* studies have shown that imiquimod has no direct antiviral effects, the drug does exhibit antiviral and antitumor effects *in vivo* through induction of cytokines in human peripheral blood monocytes (PBMC) and enhancement of cell-mediated cytolytic antiviral activity.^(12, 23)

Imiquimod, and its analogs R-842, S-27609, and S-28463, are potent anti-viral and anti-tumor agents in animal models.^(12, 17-18) Much of the biologic activity of these compounds can be attributed to stimulate the innate immune response through the induction of cytokines and the cellular arm of acquired immunity, including interferon-alpha (IFN-alpha), interferon-gamma (IFN-gamma), tumor necrosis factor-alpha, interleukins-1, -6, -8, -12 and others. According to the animal model study, the concentrations of interferon and tumor necrosis factor were higher at the site of drug application than in skin from the contralateral flank or skin from untreated animals. Interferon-alpha mRNA levels were also elevated in the skin of animal after topical application of either imiquimod or S-28463. *In vitro*, both imiquimod and S-28463 induced increases in interferon and tumor necrosis factor in cultures of cells isolated from animal skin.^(16 - 17, 19) Imiquimod also increases interleukin-8 concentrations in human keratinocyte and fibroblast cultures, whereas S-28463 induced increase in tumor necrosis factor in fibroblast cultures.^(18, 24) But it

did not induce the transcriptional expression of inflammatory cytokines in human first trimester placental trophoblasts.⁽¹³⁾

Keratinocyte differentiation coordinates the balance between positive and negative signals along the Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway by regulating the interferon response factors (IRF1:IRF2) and STAT1:PIAS1 ratios and thus affecting induction of imiquimod-inducible genes. Specifically, differentiation supports constitutive expression of STAT1 and IRF1 mRNAs but not expression of IRF2 and PIAS1. Hence, the importance of STAT1 in cytokine induction and activation of interferon-responsive genes by imiquimod is stated⁽¹⁸⁾ (Figure 2). Therefore, stimulation of production of cytokines by imiquimod in the skin after topical applications, may play a major role in its activity in genital wart patients.^(12 - 25)

Results from animal studies have also indicated a possible use for imiquimod in the prevention and treatment of other cutaneous viral infections such as herpes simplex infection and molluscum contagiosum infection. In addition, recent studies demonstrated that imiquimod activates Langerhans' cells (LC) migration from skin to draining lymph nodes and enhances allergic contact hypersensitivity.^(12 - 25) These data indicate that imiquimod dissociate the functional maturation (cytokine-mediated) and phenotypic maturation of epidermal LC. The present exploration topic is to use the adjuvant activity of imiquimod to introduce imiquimod-treated Langerhans' cells for processing and presentation of viral peptides to Th-lymphocytes as a novel vaccine strategy to induce protective antiviral responses.

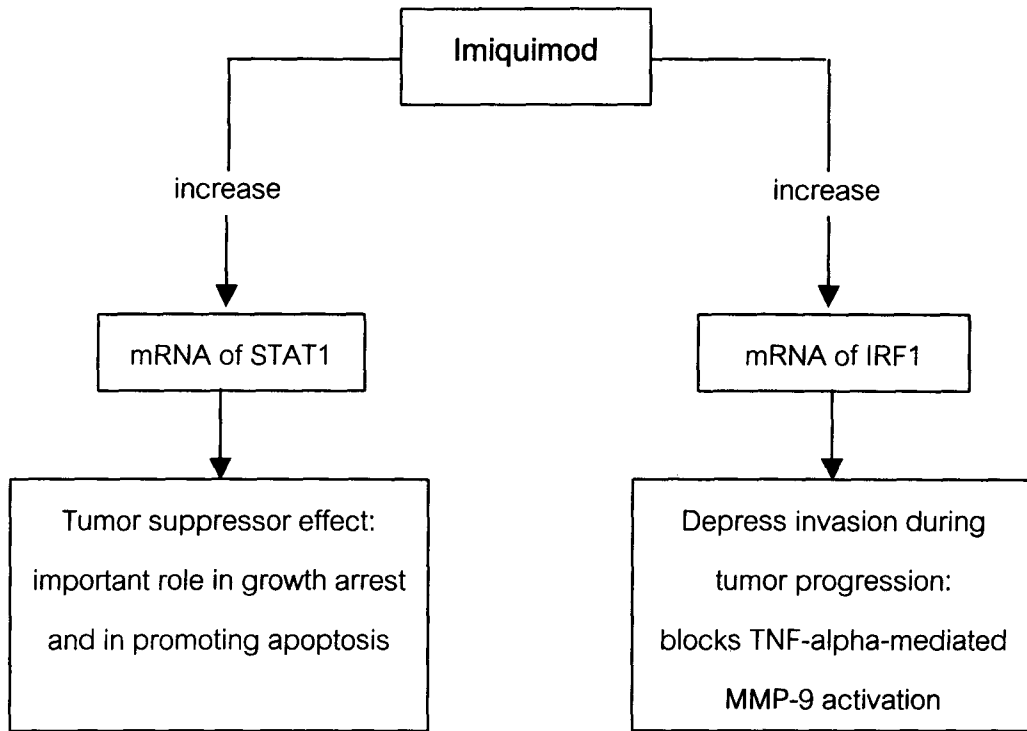


Figure 2. Summative diagram demonstrating the effect of imiquimod on JAK/STAT pathway.

4. Pharmacoeconomic aspect ⁽²⁶⁾

It becomes clear that in cost per sustained clearance terms, imiquimod, as first-line therapy, is the most cost-effective intervention comparing to other first-line or second-line option therapies. Therefore, consideration to use imiquimod cream as the first regimen for anogenital warts therapy is set, due to the cost effectiveness.

Usage information

1. Indication and contraindication ⁽⁵⁾

The major indication of imiquimod cream is for external genital, perianal warts and *condyloma accuminata*. It is used to treat the warts on surface of the penis or vulva and around the anus. No absolute contraindication is mentioned. But no specific information from clinical trials for treatment of viral

infections at other sites is reported. Therefore, it is now not recommended for usage for vaginal, cervix, rectal and anal infection. ⁽⁵⁾

2. Dosage

It is to be applied once a day, at bedtime; three times a week. ⁽⁵⁾ Application of a thin layer of the cream onto clean, dry wart area until the cream vanishes is recommended. Washing is allowed after leaving the cream applied on the lesion for 6 to 10 hours. Sexual contact of any forms should be avoided because the effect of the ingredient on the transmission of the wart is not already studied and it can weaken condoms and vaginal diaphragms during sexual activity.

Treatment with imiquimod cream should be continued until the warts are completely disappeared.

More than 16 weeks of usage is not recommended. Generally, it takes 8 to 10 weeks, sometimes as early as 4 weeks, to clear the lesion.^(2-3, 5, 12) Due to the length of therapy, some patients may discontinue the treatment which can be a major disadvantage of this preparation. If this is the case, the frequency of application should not be amended from the recommended regime of 3 times a week due to the report of increasing of dermatological side effects from too often applications.

3. Specific precaution^(5, 22)

There is no report on carcinogenesis and mutagenesis from testing imiquimod in an animal model study. Imiquimod is not recommended for use in children under the age of 12 years and for mothers who do breast feeding or intend to breast feed, as there have been no studies of its effects on children and there has been no report about excretion into the breast milk. It is also not administered to pregnant women, as there have been no studies of its effects on pregnant subjects. In an animal model study, the 28 times fold dosage of that normally used in human beings can cause low birth weight and defect in bone forming in rat fetus.^(5, 22) Using imiquimod concomitantly with other preparations to treat warts is not proved for its drug interaction side effects, and therefore not recommended.

4. Adverse effect⁽²⁷⁻²⁸⁾

The dermatological side effect at the lesion is the most common reported side effect of imiquimod (prevalence less than 70 %).⁽²⁷⁻²⁸⁾ Redness, ulceration, indurations, excoriation, flaking and edema are described. Most of these skin reactions are often mild

to moderate. Local erythema and itching (about 50 % of overall side effect) is the most common adverse reaction^(5, 27-28), but the majority of patients developed no side effect or only mild local inflammatory reactions. Severe skin reaction can be observed in the case of overdose. *Tinea cruris*, myalgia, fever, nausea, vomiting and headache can also be observed.^(1-3, 5, 27-28) This systemic reaction is believed to be due to the immunomodification action of the active ingredient. However, there was no difference in incidences of flu-like symptoms compared to other treatment methods.⁽²⁷⁾ No hepatic or renal toxicity or other hematological changes exceeding the normal range were mentioned.

Clinical application of imiquimod

1. Genital wart^(5, 29-34)

Since imiquimod is a cytokine inducer, it has been successfully used in the treatment of genital warts, a common sexual transmitted disease. Numerous clinical trials have shown topical imiquimod to be effective and safe for the treatment of anogenital warts.⁽²⁹⁻³⁴⁾ In addition, in clinical settings, patients responded well and wart recurrence rates appear to be lower (about 10 %) than those reported for many standard therapies of genital warts.⁽²⁹⁻³⁴⁾ The response rate varies from 75 to 100 %.⁽²⁹⁻³⁴⁾

From analysis of the levels of expression of genes of the JAK/STAT signaling pathway and their inhibitors as well as IRFs in pretreatment biopsy specimens by reverse transcription-PCR, it is revealed that mRNA levels of signal transducer and activator of transcription 1 (STAT1) and IRF1 were higher in complete responders (99 to 100 % wart reduction rate) than in incomplete responders (75 to 92 % wart

reduction rate). Incomplete responders expressed larger amounts mRNA of STAT3, IRF2, and protein inhibitor of activated STAT1 (PIAS1) mRNAs compared to complete responders before imiquimod treatment. Therefore high-level expression of STAT1 and IRF1 is advantageous for a better response.⁽¹²⁻²⁵⁾

Treatment with imiquimod significantly increases the mRNA level for interferon (IFN)-alpha, IFN-gamma and 2',5' oligoadenylate synthetase (2',5'-AS) as well as a tendency towards the increase of tumor necrosis factor (TNF)-alpha and interleukin-12 p40. Significant increases in mRNA for CD4 and a trend toward increases in CD8 are also observed in imiquimod-treated patients. Imiquimod administration is also associated with a significant decrease in viral load as measured by HPV DNA and L1 mRNA. The effects on HPV markers are believed to be accompanied by an apparent decrease in mRNA expression for markers of cell proliferation and an increase in mRNA levels for markers of keratinocyte differentiation and tumor suppressors (Table 1).

From, randomized, double-blind, placebo-controlled studies, tropical imiquimod cream is effective and safe a self-administered therapy for external anogenital warts when applied 3 times a week overnight for up to 16 weeks. Furthermore, patients who received tropical imiquimod cream experienced more eradication (about 50 %) of all treated baseline warts than other routine methods.

Comparing to other currently available methods for clearance of visible genital warts lesions, the current failure rate, recurrence rate, and side-effects of these treatments are satisfactorily low.⁽²⁹⁻³⁴⁾ Imiquimod can be used as patient self-directed regimen.^(2-3,5) However, significant issues in the use of this preparation included: firstly, patient education- especially for those who had previously received ablative therapy; secondly, the length of time that therapy would be continued before the patient was deemed to be a non-responder to Imiquimod cream. Good patient compliance should be set.

Table 1. Summary of immunomodulating effects of imiquimod.

Decrease	Increase
1. viral load as measured by HPV DNA and L1 mRNA	1. mRNA level for interferon (IFN)-alpha, IFN-gamma and 2',5' oligoadenylate synthetase (2',5'-AS)
2. mRNA expression for markers of cell proliferation	2. tumor necrosis factor (TNF)-alpha and interleukin-12 p40
	3. mRNA for CD4 and CD8
	4. mRNA levels for markers of keratinocyte differentiation and tumor suppressors

2. Other viral skin lesions

Clinical experience with this medication since its availability 2 years ago has shown that it is important in the therapy of genital wart. However, the antiviral and antiproliferative effects of imiquimod, as well as early reports, indicate that this medication may prove to be useful in the treatment of other skin diseases, including some nongenital warts and molluscum contagiosum.⁽³⁵⁻³⁷⁾ There is a strong scientific rationale to suggest that imiquimod may be useful in the treatment of a variety of cutaneous viral diseases such as herpes zoster (varicella zoster virus) and molluscum contagiosum that have been shown to respond to immunomodulatory drugs. Considering herpes simplex virus (HSV) infection, imiquimod is currently in clinical trials for treating human HSV infections. But in an animal model, the cure rate of this disease is only fair.^(38 - 42) It represents a new approach in the therapeutic treatment paradigm for treatment of cutaneous viral diseases at their site of infection.

3. Basal cell carcinoma^(43 - 45)

Imiquimod cream has been used effectively in eradicating superficial basal cell carcinomas (BCCs), a carcinoma responding to interferon therapy. Toleration to the treatment is accepted by the patients though the length of treatment time and the some local inflammation at the treatment sites. For other cancer treatment, oral form of imiquimod regimen is in the clinical trial phase.⁽⁴⁶⁾

4. Cutaneous Leishmaniasis⁽⁴⁷⁾

Leishmaniasis, a tropical infectious disease caused by *Leishmania* protozoa and is a major cause

of suffering and morbidity in much of the developing world. Since imiquimod activates a number of immune cells, including macrophages, which are the only host cells of *Leishmania* species, an investigation in mouse model shows that imiquimod can effectively stimulate leishmanicidal activity in macrophages; moreover, imiquimod stimulates signal transduction associated with inducing nitric oxide synthesis in macrophages. Therefore, imiquimod can be a trend for treatment of Cutaneous Leishmaniasis.⁽⁴⁷⁾

5. Virus-induced airway dysfunction⁽⁴⁸⁾

Viral respiratory infections cause acute airway abnormalities consisting of inflammation and physiological dysfunction in both animals and humans. From an animal model study, it revealed that imiquimod can induce interferon-alpha, and attenuate the development of airway dysfunction during acute viral illness in rats. Therefore, more specific pharmacological interventions of imiquimod can be developed for the treatment of virus-induced asthma in humans.⁽⁴⁸⁾

Imiquimod for treatment of viral skin lesions in HIV-infected patients.

Good and safe therapeutic effects of imiquimod cream in HIV – infected patients with various cutaneous viral infections including anogenital warts, herpes zoster (varicella zoster virus), oral hairy leukoplakia (Epstein-Barr virus), Kaposi's sarcoma (HHV-8), molluscum contagiosum, plantar warts (HPV-1), facial warts and flat warts (HPV-5) were mentioned.^(49 - 50) From a clinical study, biologic responses, measured by elevations in serum circulating interferon, beta2-microglobulin, and

neopterin levels with variable effect on virus load in asymptomatic HIV-infected persons can be observed.^(49 - 50) Same dose-limiting toxicities as detected in normal subjects including fatigue, fever, malaise, increased transaminases, hypotension, vomiting, and depression were also revealed. Immunomodulatory activity of the imiquimod can be an effective tool in treatment of cutaneous viral infection among HIV –infected patients where the lymphocytes, critical regulatory and effector cells of the immune system, are progressively destroyed.⁽⁵⁰⁾

1. Genital wart ^(51 - 53)

This immunomodulatory agent is also mentioned to be safe and effective in the management of anogenital warts in patients with human immunodeficiency virus (HIV) infection. Topically applied imiquimod 5 % cream can effectively reduce wart area. Most local skin reactions were mild and no adverse effects on HIV disease were observed.

2. Molluscum contagiosum ^(54 - 55)

Molluscum contagiosum is a common cutaneous infection complicating the course of patients afflicted with acquired immunodeficiency syndrome. Conventional cytotoxic therapies always fail to clear the lesion in these patients, but imiquimod 5 % cream, is reported to have the ability to clear clinically this cutaneous disease.

3. Facial wart ^(56 -58)

Facial wart or facial verrucae is a common viral cutaneous infection among HIV-infected patients. Successful treatment with topical 5 % imiquimod cream of facial papillomatosis in an individual with

human immunodeficiency virus infection is mentioned.

Conclusion

Imiquimod (1-(2-methylpropyl)-1H-imidazo [4,5-c]quinolin-4 amine), is a topically active immunomodulatory agent that is formulated as a 5 % cream for application by the patient. It is the first agent of its class used in the treatment of genital warts. Its potent antiviral and antitumor activity via induction of human cytokines can be demonstrated. In immunocompetent patients with genital warts, imiquimod stimulates the production of interferon-alpha and various other cytokines, and has indirect antiviral activity. The activity of this drug results primarily from interferon alpha (IFN-alpha) induction and other cytokine induction.^(30 -34) These cytokines stimulate several other aspects of the innate immune response. In addition, imiquimod stimulates acquired immunity, in particular the CD4 and CD8, which is important for the control of viral infections and various tumors.^(30 - 34)

From previous clinical trials,^(30 - 34) good clearance rate of warts occurred in 37 to 50 % of immunocompetent patients with genital warts treated with imiquimod 5% cream 3 times a week for up to 16 weeks. Recurrence of wart occurred in less than 20 % of immunocompetent patients in whom complete clearance of warts had been achieved with this regimen.^(30 -34) Imiquimod 5 % cream also shows good clearance of warts in immunosuppressed HIV-infected patients with genital warts.^(51 - 53) Imiquimod cream is generally well tolerated by both immunocompetent and HIV-infected patients. Local skin reactions (mainly mild or moderate), including erythema, itching and burning, are the most commonly reported adverse

events, occurring in less than 70 % of patients applying imiquimod 5 % cream 3 times a week.^(27 - 28)

Imiquimod cream is, therefore, a new therapeutic option for patients with genital warts. Moreover, in contrast to most alternative treatment strategies, which are administered in the physician's office, imiquimod cream is a self-administered therapy for outpatient use.

Furthermore, imiquimod is expected to be effective where exogenous IFN-alpha has shown utility and where enhancement of cell-mediated immunity is needed. Also, the mechanism of action of topically applied imiquimod is likely to benefit the cure of several other chronic viral infections and tumors of the skin.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์
กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย
ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง
“อิมิควิโมด ยานชนิดใหม่ กลุ่มออกฤทธิ์ผ่านกลไกทางภูมิคุ้มกัน” โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่า
ถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก <http://www.ccme.or.th>

คำถาม - คำตอบ

1. Which is not the effect of imiquimod ?
 - A. decrease HPV viral load
 - B. increase mRNA expression for cell proliferation markers
 - C. increase mRNA for several IFN
 - D. increase mRNA for CD4
 - E. increase TNF
2. Which cancer has been documented to be effectively managed by imiquimod
 - A. melanoma
 - B. squamous cell carcinoma
 - C. basal cell carcinoma
 - D. liposarcoma
 - E. cholangiocarcinoma
3. Which is the major indication for imiquimod application
 - A. acne
 - B. pityriasis rosea
 - C. molluscum contagiosum
 - D. genital wart
 - E. chicken pox

✂

คำตอบ สำหรับบทความเรื่อง “อิมิควิโมด ยานชนิดใหม่ กลุ่มออกฤทธิ์ผ่านกลไกทางภูมิคุ้มกัน”

จุฬาลงกรณ์เวชสาร ปีที่ 48 ฉบับที่ 5 เดือนพฤษภาคม พ.ศ. 2547

รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/0305-(1008)

ชื่อ - นามสกุลผู้ขอ CME credit เลขที่ใบประกอบวิชาชีพเวชกรรม.....
ที่อยู่.....

1. (A) (B) (C) (D) (E)

4. (A) (B) (C) (D) (E)

2. (A) (B) (C) (D) (E)

5. (A) (B) (C) (D) (E)

3. (A) (B) (C) (D) (E)

4. What is the main side effect of imiquimod
- A. carcinogenesis
 - B. genotoxic
 - C. cardiotoxic
 - D. nephrotoxic
 - E. local irritation
5. Which is not the composition of imiquimod cream
- A. xanthan gum
 - B. ISA
 - C. Sorbitan monoesterase
 - D. Polysorbate 60
 - E. Quinolone -4-amide

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหลัง

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