Topical hexaminolevulinate photodynamic therapy for the treatment of persistent human papilloma virus infections and cervical intraepithelial neoplasia

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Introduction: Current treatments for high-grade cervical intraepithelial neoplasia (CIN2/3) are mainly excisional procedures, which are associated with significant side effects and pose risks for future pregnancies. An effective and safe therapy is needed to reduce the requirement for surgical interventions in women of reproductive age.

Areas covered: This review looks at the pharmacokinetic and clinical data for topical hexaminolevulinate (HAL) photodynamic therapy (PDT), which is currently entering late phase clinical trials for high-grade CIN. The authors include published studies in patients and volunteers but laboratory and animal studies have been excluded as have studies on other porphyrins such as Photofrin, 5-aminolevulinic acid, methyl aminolevulinate and studies reporting other clinical applications for HAL.

Expert opinion: Topical HAL PDT has potential as a non-surgical tissue-preserving treatment for CIN and persistent oncogenic human papilloma virus infections. HAL PDT selectively treats the entire epithelial sheet, without the tissue destruction seen in excisional procedures. The authors believe that this treatment could replace surgery in a large proportion of patients. It would be of particular value to the high percentage of women who are interested in future child-bearing. If the treatment is approved, it is very likely that physicians will want to use this treatment, as many patients will be keen to consider a non-surgical option.

Keywords: cervical cancer, cervical intraepithelial neoplasia, hexaminolevulinate, human papilloma virus, photodynamic therapy


1. Introduction

1.1 Disease background
Cervical cancer is the third most common cancer in women worldwide, responsible for 275,000 deaths each year, mainly in countries with less well-developed cervical cancer screening programmes [1]. However, the prevalence of cervical intraepithelial lesions is comparable. Persistent infection with oncogenic human papillomavirus (HPV) genotypes, particularly high-risk types HPV16 and HPV18, is responsible for virtually all cases of cervical cancer [2].

HPV is the most prevalent sexually transmitted infection, with a peak prevalence of 25 – 35% in young women. It is estimated that at least 70% of all women will be infected with HPV during their lifetime [3]. In newly infected women, there is a high spontaneous regression rate of 90% within 2 years, but in the remaining 10%, infections can persist [4]. When oncogenic HPV infection of the cervical epithelium
2. Treatment review

2.1 Market overview

2.1.1 Problems with currently available therapies

The main drawbacks with current treatments are the significant side effects and the risks posed for future pregnancies. Even procedures considered to be less destructive, such as cryotherapy, are associated with uterine cramps, fainting, vaginal discharge and unsatisfactory colposcopy following treatment [12].

Surgical conisation, using either a cold knife, LEEP or laser, increases the risk of pre-term labor, low birth weight, premature rupture of membranes and caesarean section [14-19]. There are as yet insufficient long-term data to evaluate the effect of ablative therapies on future pregnancies.

Because of these adverse consequences, and the high rate of spontaneous regression, recent US and WHO management guidelines recommend that young women with high-grade CIN should initially be managed conservatively to minimize risks in future deliveries [10,20].

2.1.2 Other treatments in development

Vaccination against HPV infection is an obvious treatment strategy but as yet HPV vaccines have not shown sufficient therapeutic effect to be considered viable alternatives to surgery [21-23].

In a recent study of imiquimod, a topically applied immune-response modulator, patients with CIN2 and 3 had a histologic regression of 73% compared with placebo (39%, p = 0.009) and high clearance of oncogenic HPV (60% compared with 14%, p < 0.001) [24]. Imiquimod had been found to be effective in the treatment of HPV-related vulvar intraepithelial neoplasia [25] but the trial in CIN was relatively small [26] and larger trials are needed to confirm these findings. The product has to be administered for several weeks and patients report undesirable side effects.

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**Box 1. Drug summary.**

<table>
<thead>
<tr>
<th>Generic drug name</th>
<th>Hexaminolevulinate hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>III</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>The indication will be for patients with persistent oncogenic human papilloma virus and low-grade squamous intraepithelial lesions or high-grade squamous intraepithelial lesions (squamous intraepithelial lesions of low- or high-grade). Hexvix® (Cysview® in the USA) 85 mg containing HAL is currently registered for the detection of bladder cancer in Europe and the USA.</td>
</tr>
<tr>
<td><strong>Pharmacology/mode of action</strong></td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Topical</td>
</tr>
<tr>
<td><strong>Chemical structure</strong></td>
<td></td>
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</tbody>
</table>

\[
\text{OCH}_2\text{(CH}_2\text{)}_4\text{CH}_3
\]

| **Pivotal trials** | [35,36,38-40] |

CIN1 is also referred to as low-grade squamous intraepithelial lesions (LSIL), and CIN2 or CIN3 (previously known as moderate dysplasia and severe dysplasia/carcinoma *in situ*) are also referred to as high-grade squamous intraepithelial lesions (HSIL) [6,7].

While slight variations exist across different age strata, low-grade CIN (CIN1) regresses in the majority of patients with a low risk of progression to CIN3 (10%) or cancer (<1%), whereas CIN2 carries a slightly higher risk of progression. CIN3 lesions can regress in up to 30% of patients; however, 30% can progress to cancer [8,9].

### 1.2 Current management practice

The aim of patient management is to minimize the risk of progression to invasive cancer while avoiding overtreatment and complications. Treatment is not recommended for patients with CIN1 due to a high spontaneous rate of regression; instead, patients are monitored regularly with cervical cytology, HPV testing and, when indicated, colposcopically directed biopsies. Women with low-grade disease persisting for 2 years may be considered for treatment with ablation or excision procedures [10,11].

Incident CIN2, especially in young women, can be followed with regular observation, otherwise treatment is recommended. CIN2 and CIN3 which have not regressed are commonly treated either with ablation or excision to remove abnormal epithelial cells. Ablation techniques including cryotherapy, laser vaporisation or electrocauterization may be used for smaller lesions. Ablative techniques do not allow for a sample of tissue to be taken for analysis and may therefore not be suitable for larger areas of tissue identified as CIN3 [12].

Excisional treatments include loop electrosurgical excision procedure (LEEP), laser conisation and surgical conisation. LEEP is carried out with a fine low voltage wire loop, which removes abnormal tissue; conisation is the removal of a cone or cylinder-shaped piece of tissue either with a scalpel or laser. Ablative and excisional techniques are thought to be equally effective at reducing the risk of progression to invasive disease. However, excision is generally recommended in order to obtain tissue for pathologic analysis to rule out invasive cervical cancer [13].

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**Chemical structure**

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\text{OCH}_2\text{(CH}_2\text{)}_4\text{CH}_3
\]
Other agents such as cyclooxygenase-2 inhibitors [27], indole-3-carbinol [28] and anti-virals [29] have been studied in women with cervical neoplasia with some promise. However, none of these medical therapies has so far been introduced into clinical practice [30]. An effective and safe therapy is clearly needed to reduce the requirement for surgical interventions in women of reproductive age [31].

Topical hexaminolevulinate (HAL) (Photocure ASA, Hoffsvieen 4, NO-0275, Oslo, Norway) photodynamic therapy (PDT) has the potential to address the medical need for a tissue-preserving treatment of persistent oncogenic HPV infections and CIN. HAL PDT selectively treats the entire epithelial sheet, without the tissue destruction seen in excisional procedures.

2.2 Introduction to treatment
HAL PDT using an intravaginal light-delivery device (Cevira®) has been investigated for the treatment of CIN and has shown promising results.

In the treatment of CIN, HAL is administered via the photoactivation device (Figure 1), which is inserted in an outpatient procedure. The patient may then carry out normal daily activities while wearing the device. After 5 h contact with the drug, the single-use device automatically delivers 100 J/cm² of red light, over a period of 4.6 h before being removed by the patient once treatment has been completed.

2.3 Chemistry
HAL is the n-hexyl ester of 5-aminolevulinic acid (5-ALA) and it is used as the hydrochloride salt. The structure is shown in Figure 2.

HAL is formulated as an ointment in a base of medium chain triglycerides and stearic acid.

2.4 Pharmacodynamics
PDT requires accumulation of a photoactive compound in target cells, which are then illuminated to generate highly reactive oxygen species that induce apoptosis and necrosis. Ideally, effects will be local and confined to the epithelium, will preserve underlying tissue and will have minimal residual skin sensitivity.

5-ALA is the endogenous early precursor in the biosynthesis of heme (Figure 3). Photoactive porphyrins (mainly protoporphyrin IX [PpIX]) are intermediates in the synthesis of heme. Exogenous administration of HAL leads to the selective accumulation of PpIX and other photoactive porphyrins in CIN compared with normal cervical tissue, partly due to the limited enzyme capacity of ferrochelatase in pre-malignant cells.

When excited by light of a specific wavelength, photoactive porphyrins enter into a higher energy state. Upon release of the energy, tissue oxygen is transformed into singlet oxygen, bringing about phototoxic effects on tissue in the immediate vicinity. The primary cause of cell death after PDT is likely to be due to mitochondrial damage or dysfunction, leading to apoptosis and necrosis [32].

2.5 Pharmacokinetics and metabolism
Two clinical studies have investigated the pharmacokinetics of porphyrin accumulation in CIN and one study in volunteers has investigated systemic availability of HAL after topical administration.

An early study by Andrejevic-Blant et al. aimed to determine whether PpIX was selectively accumulated by dysplastic cells of the cervix [33]. HAL HCl (3 g, 0.5%) was applied topically to the cervix for various periods of time by means of a cervical cap, and random biopsies were taken between 5 min and 7 h. Standard histological analysis and fluorescence microscopy in healthy tissue and CIN were used to assess the distribution of PpIX. In dysplastic lesions, there was a fluorescence ratio of 4 – 5 in the epithelium relative to underlying lamina propria after an application time of 2 – 6 h (Figure 4).

Pharmacokinetics and tissue selectivity were investigated by Hillemanns et al. in 24 patients with CIN lesions [32]. Ten millilitres of HAL HCl 0.1 and 0.25% solutions were applied to the cervix for 5 min to 12 h before surgical conisation. Fluorescence microscopy was carried out on segments of the excised tissue, evaluating the intensity at 635 nm for porphyrin fluorescence and 600 nm for autofluorescence. Phototoxic porphyrin fluorescence was significantly higher in neoplastic tissue compared with normal epithelium and underlying lamina propria and it increased with time of exposure to the agent. Porphyrin fluorescence reached a peak between 3 and 9 h after application. There was selective accumulation of photoactive porphyrins in pre-malignant cervical epithelium relative to normal adjacent epithelium.

A pharmacokinetic study in volunteers using 14C-labelled HAL [34] found that there was a limited bioavailability of 8 – 10% following topical administration and the major route of excretion was via urine (Photocure Internal Report, unpublished).

2.6 Clinical efficacy
Data are available from four clinical studies using topical administration of HAL HCl, different HAL formulations (solution, suppository and ointment) and two photoactivation systems (laser and light-emitting diode [LED]).

2.6.1 Phase I studies
In a pilot feasibility study carried out in 24 women with histologically verified CIN1 – 3 lesions and oncogenic HPV infections 35, HAL HCl gel (10 ml, 0.25%) was applied with a cervical applicator and left for 3 – 5 h before photoactivation with a red laser (635 nm, illumination time 17 min and light dose 100 J/cm²). Patients were assessed for response 3 – 6 months after PDT, which was repeated for partial responders.

There was a complete response rate of 63% (15/24), as assessed by histology, cytology and HPV clearance, and one partial response. Lesion clearance was similar in the three
groups: 71% (5/7), 50% (5/10) and 71% (5/7) for CIN1, 2 and 3, respectively. The morphology of the ectocervix was maintained and there were only minor self-limiting local side effects [35].

2.6.1.1 Study CE101/06
A Phase I/II randomized dose-finding study investigated HAL and the methyl ester of 5-ALA in various dose and light groups and two incubation periods in 92 patients with CIN1 - 3 [36]. In patients with CIN2 and 3, the optimal procedure was 40 mM of HAL HCl (100 mg, 1%) applied for 3 h, and activated with 50 - 100 J/cm² light dose (635 nm). In this group, there was a complete response rate after 6 months of 57% (30/53) - 83% (20/24) in the CIN2 group - and oncogenic HPV infection was cleared in 67% (10/15) of patients, with a pathological remission.

A morphological analysis of normal tissue biopsies from 25 patients found no significant macroscopic changes of the cervix, and histological evaluation revealed no signs of apoptosis, necrosis, irritation, vascular changes or fibrosis with PDT 6 months after treatment [37].

2.6.2 Phase II studies
2.6.2.1 Study CE201/08
A double-blind, randomized, placebo-controlled study in 70 patients with CIN1 [38] used HAL HCl (2 g, 5%, n = 47) or a placebo vaginal suppository (n = 12) with an application period of 5 h, before laser photoactivation with a 50 J/cm² light dose, and a second control group that received follow-up only (n = 11). Response 6 months after treatment in the per-protocol group was 57% (20/35) in the HAL PDT group and 25% (5/20) in the combined control group (p = 0.04). Eradication of high-risk HPV was achieved in 73% (11/15) patients in the active group.

In an extension to the study, the feasibility of the newly developed treatment procedure including Cevira ointment and device was assessed in 13 patients with CIN1 or 2 [39]. At 6 months, 9/10 patients in the HAL PDT group had normal biopsy or colposcopy and normal cytology, compared with 1/3 in the control group. Patients who showed histological regression did not subsequently progress and only very few patients who experienced HPV clearance developed a recurrent infection with the same HPV subtype. The device was considered very acceptable by patients and easy-to-use by gynecologists.

2.6.2.2 Study CE203/10
A double-blind, placebo-controlled dose-finding Phase IIb study was carried out in 262 patients with CIN1 or 2 randomized to HAL HCl 0.2% (4 mg), 1% (20 mg) or 5% (100 mg) or placebo [40]. A total light dose of 100 J/cm² was delivered over 5 h using an LED-based photoactivation system (Table 1). One re-treatment was permitted at 3 months in women with positive histology or cytology.

Based on central histology read, there was a significant difference between HAL 5% and placebo 3 months after the last treatment (including re-treatments) in the CIN2 group: 94.7% (18/19) versus 57.1% (12/21, p = 0.009) and the response was sustained at 6 months (94.7 vs 62%).

In the CIN2 group, initial oncogenic HPV clearance was 62% (8/13) in the 5% HAL group compared with 28% (5/18) in the placebo group. Interestingly, there was good clearance of high-risk HPV 16/18: 83.3% (5/6) in the HAL
5% group at 3 and 6 months, compared with 0 and 33.3% (0/6 and 2/6) in the placebo group. The HAL PDT response in the CIN1 population was not significantly different to that of the placebo group, due to a high rate of spontaneous regression in the CIN1 population. This was probably caused by the inclusion of oncogenic HPV-negative patients. The safety profile of HAL PDT was favorable with mainly local, self-limiting side effects that resolved within a few days of treatment. There were no signs of systemic effects. The device was easily administered by the gynecologist and removed by the subjects.

2.6.3 Phase III studies

In planning phase, none has been carried out yet.

2.6.4 Post-marketing surveillance

Not applicable.

2.7 Safety and tolerability

Safety data are available from six clinical studies involving over 400 patients and at least 500 treatments.

HAL PDT treatment has demonstrated an excellent safety profile with mainly mild-to-moderate local reactions and no serious adverse reactions. The reported adverse reactions were mainly self-limiting and included discharge, discomfort and spotting. Most resolved within a few days. No overdose or significant toxicity has been reported or is expected with topical application of HAL HCl.

Systemic adverse reactions have been uncommon. While a causal relationship could not be excluded for all the systemic adverse events, there was no pattern which could indicate systemic toxicity. There is also no indication that HAL administration to the cervix results in dermal phototoxicity reactions.

Reproduction and developmental toxicity studies have shown no embryo-fetal safety findings of concern. During the clinical programme, nine women became pregnant, eight of whom gave birth to normal infants while one woman had a missed abortion considered not related to study treatment. HAL is also the active ingredient in Hexvix® (Cysview®), which is used in the diagnosis of bladder cancer. This product is administered topically with the same dose as for CIN (100 mg HAL HCl) and has a similar low systemic absorption of 8–10%. Apart from a few cases of hypersensitivity reaction, there are no clusters of specific reactions that indicate any additional risk to patients receiving HAL in this setting. The use of this product in more than 250,000 patients supports the safe use in this application.

2.8 Regulatory affairs

HAL PDT using the intravaginal light-delivery device is in late phase clinical development in women with persistent oncogenic HPV/CIN and has not yet been approved in any country.
Table 1. Studies with topical hexaminolevulinate photodynamic therapy for cervical intraepithelial neoplasia.

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Study design</th>
<th>Population</th>
<th>Drug formulation</th>
<th>Photoactivation</th>
<th>Patient response</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Open, pharmacokinetic</td>
<td>27 patients with CIN1 - 3</td>
<td>Topical HAL HCl 0.5% 5 - 420 min</td>
<td>No photoactivation</td>
<td>Not applicable</td>
<td>No side effects reported</td>
</tr>
<tr>
<td>I</td>
<td>Open, pharmacokinetic</td>
<td>24 patients with CIN1 - 3</td>
<td>Topical HAL HCl 0.1 - 0.25% 5 - 720 min</td>
<td>No photoactivation</td>
<td>Not applicable</td>
<td>No side effects reported</td>
</tr>
<tr>
<td>I</td>
<td>Open, 6 months</td>
<td>24 patients with CIN1 - 3</td>
<td>Topical HAL HCl 0.25% 3 - 5 h</td>
<td>Laser 635 nm 100 J/cm²</td>
<td>15/24 (63%) in CIN1 - 3</td>
<td>50% of patients reported mild-to-moderate vaginal discharge</td>
</tr>
<tr>
<td>VII</td>
<td>Blinded, randomized, dose-finding, 6 - 12 months</td>
<td>92 patients with CIN1 - 3</td>
<td>Topical HAL HCl 0.25 - 1% and methyl aminolevulinate 20%, 1 - 12 h</td>
<td>Laser 635 nm 25 - 100 J/cm²</td>
<td>20/24 (83%) in CIN1/2 with 3 h application and 50 - 100 J/cm²</td>
<td>68% of patients reported mild-to-moderate local events including vaginal discharge and uterine cramping</td>
</tr>
<tr>
<td>I</td>
<td>Open, pharmacokinetic study</td>
<td>8 healthy subjects</td>
<td>Topical HAL HCl 5% 5 h and intravenous bolus 0.4 mg/kg</td>
<td>No photoactivation</td>
<td>Not applicable</td>
<td>No systemic or local side effects reported</td>
</tr>
<tr>
<td>Ila</td>
<td>Double blind, randomized, placebo controlled, 6 months</td>
<td>70 patients with CIN1</td>
<td>Topical HAL HCl 5% 5 h</td>
<td>Laser 635 nm 50 J/cm²</td>
<td>20/35 (57%) versus 4/16 (25%) in CIN1</td>
<td>37% of patients reported mild-to-moderate local events including vaginal discharge and uterine cramping</td>
</tr>
<tr>
<td>Ila</td>
<td>Double blind, randomized, 6 months</td>
<td>13 patients with CIN1/2</td>
<td>Topical HAL HCl 5% 5 h</td>
<td>LED 629 nm 100 J/cm²</td>
<td>7/10 (70%) versus 1/2 (50%) on placebo in CIN1/2</td>
<td>23% of patients reported mild-to-moderate local side effects including vaginal discharge and pain</td>
</tr>
<tr>
<td>IIb</td>
<td>Double blind, randomized, dose-finding, placebo controlled 9 months</td>
<td>262 patients with CIN1/2</td>
<td>Topical HAL HCl 0.2 - 5% 5 h</td>
<td>LED 629 nm 100 J/cm²</td>
<td>18/19 (95%) versus 12/21 (57%) on placebo in CIN2</td>
<td>38% of patients reported mild-to-moderate local side effects including vaginal discomfort, discharge and spotting</td>
</tr>
</tbody>
</table>

CIN: Cervical intraepithelial neoplasia; HAL: Hexaminolevulinate; LED: Light-emitting diode.
HAL has been prepared as an ointment to be used in conjunction with the intravaginal drug delivery system. This treatment is a drug-device combination regulated as a medical product.

HAL HCl (Hexvix/Cysview) has already been approved worldwide including the USA and Europe for topical use in the bladder to improve diagnosis and management of bladder cancer.

3. Conclusion

PDT with HAL and the new integrated intravaginal device has a favorable efficacy and safety profile and is a promising tissue-sparing alternative to observation and surgical procedures in patients with CIN, avoiding many of the side effects related to excision and ablation. More clinical data from randomized studies are required to verify this new treatment.

4. Expert opinion

In contrast to the progress which has been made in the prevention of cervical cancer through primary prevention with HPV vaccines and the introduction of high performance screening strategies using molecular testing for HPV DNA, treatment for pre-cancerous lesions still relies on surgical intervention such as LEEP, cone biopsy or laser excision.

Cold knife conisation is often used where larger amounts of epithelial and stromal tissue are to be excised. However, all surgical procedures carry a risk of late abortion, pre-term delivery and other perinatal complications. Hence, recent US management guidelines advocate conservative management in young women with CIN2/3.

There is an urgent clinical need for a non-surgical alternative. To date, conservative approaches using therapeutic vaccines have not achieved clinical efficacy. In our view, HAL PDT (Box 1) has the potential to be an effective therapy, especially for the high percentage of treated women who are of child-bearing age.

Studies have shown that porphyrins induced by the application of HAL can be detected only in the epithelium and not in the underlying cervical stroma. Therefore, PDT with HAL leads to selective treatment of abnormal epithelial cells with minimal loss, if any, of stromal tissue.

Porphyrin-based PDT removes tumour cells by inducing apoptosis and necrosis, without causing erosions or deep ulcerations such as seen with other photosensitizers. The technology has also been shown to stimulate the systemic immune system by enhancing the immune recognition of antigens. However, more research is required to understand these immunological effects which may be a crucial component in establishing long-lasting treatment effects of this virally induced pre-neoplastic disease.

The recent study by Hillemanns et al. suggests that HAL PDT using the new integrated light- and drug-delivery device has promising effects on oncogenic HPV infections and in particular on high-risk oncogenic HPV16/18 infections that carry a high risk of progression to CIN2 + lesions. The device is placed on the cervix like a diaphragm without anesthetic or pain medication, and the patient removes it 10 h later. HAL PDT, if found to be effective in clinical trials, may therefore be a viable alternative to watchful waiting or excisional treatment, particularly as the safety profile of HAL has so far been shown to be favorable. A small pilot study demonstrated that patient and gynecologist acceptance was high.

Previous studies with topically applied HAL PDT showed similar patient responses, but the procedure was inconvenient to the patient and the gynecologist. With the recent development of the device, PDT may become a practical option for out-patient treatment. It is very likely that physicians will prescribe this treatment if it is approved by the appropriate regulatory bodies as many patients will be keen to consider a non-surgical option. Robust results from large-scale Phase III studies are still needed.

Topical HAL PDT has the potential to address the medical need for a tissue-preserving treatment of persistent HPV infections and CIN, treating the entire portion of the cervix while maintaining cervical competence. More research is necessary in the field of other HPV-related lesions such as vulvar (VIN) and anal intraepithelial neoplasia (AIN), where little knowledge and few studies have been published and tissue-preserving strategies are also needed due to the morbidity of excisional procedures.

Declaration of interest

Studies with HAL PDT have been funded by Photocure, Oslo, Norway. P Hillemanns has received honoraria and research support from Photocure, while MH Einstein has advised/participated in educational speaking activities for Photocure but has not received any honorarium from any company. Montefiore Medical Center has received payment for his time spent for these activities from Photocure. Finally, OE Iversen has received lecture fees and payment as an investigator from Photocure. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Writing assistance by J Douglass of Healthcom Partners Ltd was utilized in the production of this manuscript and was funded by Photocure ASA.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


** An important paper summarizing the evidence for the causal relationship between human papilloma virus (HPV) and cervical cancer, and calling for public health action.


** Important source of information on natural course of the disease.


• Review of the literature providing a useful indication of regression, persistence and progression rates to be expected for cervical intraepithelial neoplasia (CIN)1/3.


** Important source of information on natural course of the disease.


** A significant meta-analysis that identified pregnancy-related morbidity associated with excisional procedures used to treat CIN.


** Further results from the meta-analysis in reference 16 that identified cold knife conisation and other methods used to treat CIN to be associated with perinatal mortality and serious pregnancy outcomes.


** Phase II study establishing the effectiveness of therapeutic vaccines against human papilloma virus.


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