DOI: 10.1111/j.1471-0528.2006.01041.x
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Short communication

# Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial

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*Accepted 20 June 2006.*

Conventional therapies for human papillomavirus infection aim to remove clinically apparent lesions, while latent infection may remain, representing a threat for transmission and carcinogenesis. The use of a systemic agent may more effectively control the virus. We conducted a randomised placebo-controlled study to investigate the efficacy and safety of oral inociplex in the treatment of cervical condylomata acuminata (CA) that had been resistant to conventional therapies. Thirty-eight white European women, aged 20–43 years, with genital warts of the cervix, refractory to at least one conventional therapy, were randomly assigned to receive either inosiplex, 50 mg/kg daily peros for 12 weeks (group 1), or placebo (group 2). Of the 17 evaluable group 1 women, 4 responded to the treatment completely, 7 responded partially and 6 did not respond. Of the 19 group 2 women, none responded to the treatment completely, 3 responded partially and 16 did not respond. The therapeutic difference between women receiving active and placebo therapy was statistically significant ($\chi^2 = 6.69$, $P < 0.01$) and remained significant when an intention-to-treat analysis was performed ($\chi^2 = 7.69$, $P < 0.01$). None of the complete responders experienced recurrence during the 12-month follow up. Adverse effects were mild and resolved upon completion of therapy. Compared with placebo, inosiplex showed considerable efficacy with insignificant and reversible adverse effects and without recurrences. Inosiplex may represent an efficacious and safe alternative systemic form of therapy for cervical genital warts.

**Keywords** Genital warts, human papillomavirus, inosine pranobex, methisoprinol, systemic therapy, treatment.

*Please cite this paper as:* Georgala S, Katoulis A, Befon A, Georgala C, Rigopoulos D. Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. BJOG 2006;113:1088–1091.

## Introduction

Genital human papillomavirus (HPV) infection represents an important sociomedical problem because of its high incidence and prevalence, the absence of radical therapy and, most importantly, due to its association with cervical cancer, the second most common malignancy in women worldwide.[1]

In the absence of specific anti-HPV agents, various therapeutic approaches have been tried, including chemotherapeutic or immunomodulatory agents and cytodestructive methods. Conventional management is seldom devoid of adverse effects, and it is often associated with unsatisfactory response rates and high recurrence rates.[2] Most of these methods aim to remove clinically apparent lesions, while latent HPV infection may remain. Prolonged infection represents a considerable threat for transmission and carcinogenesis, especially when oncogenic strains of HPV are involved. Thus, the use of a systemically administered agent, acting at all sites of infection, may improve the therapeutic outcome.

Inosiplex (inosine pranobex, methisoprinol, Isoprinosine®) is a synthetic compound formed from the p-acetamido benzoate salt of N,N-dimethylamino-2-propanol and inosine in a 3:1 molar ratio.[3] It is an immunomodulating agent, which has been reported to exert several immunopharmacological effects in animal and human studies, both *in vitro* and *in vivo*. Therapeutic investigations have focused primarily on viral illnesses, such as herpes simplex virus infections, subacute sclerosing panencephalitis, genital warts, influenza, zoster, hepatitis A or B and HIV infection.

We conducted a randomised placebo-controlled study to investigate the efficacy and safety of oral inosiplex in the treatment of cervical condylomata acuminata (CA) that had been resistant to conventional therapies.

## Material and methods

This study was conducted at 'A. Sygros' Hospital for Skin and Venereal Diseases in Athens from 1999 to 2003. Forty-five women with recalcitrant CA of the cervix were assessed for eligibility. The protocol was approved by the ethics committee of our hospital. Informed consent was obtained in each case.

The evaluation at entry included: history taking; clinical examination; colposcopy; Pap smear; blood counts and biochemistry profile and lesional biopsy.

Eligibility criteria included: a cytohistologically confirmed diagnosis of genital warts with at least 3-month duration; lesions refractory to conventional therapy; age older than 18 years; negative HIV serology; women in good health and with no contraindications for inosiplex administration and normal plasma uric acid values; no evidence of cervical dysplasia or malignant degeneration; no history of local or systemic anti-wart therapy or cytotoxic or immunomodulatory treatment within 4 weeks from entry.

From the 45 women assessed for eligibility, 38 women were enrolled. Seven women did not meet inclusion criteria and were excluded from the study. The women were randomised into two treatment groups, using simple randomisation. Subjects were assigned identification numbers in order of recruitment. Identification numbers corresponded to consecutive numbers derived from a random number table. A central telephone was used to implement the random allocation sequence. The sequence was concealed until interventions were assigned. The participants were enrolled and assigned to their groups by the main investigator. Subjects with table numbers 0–4 were assigned to receive oral inosiplex (group 1), while subjects with table numbers 5–9 were assigned to receive placebo (group 2), given in an equivalent number of

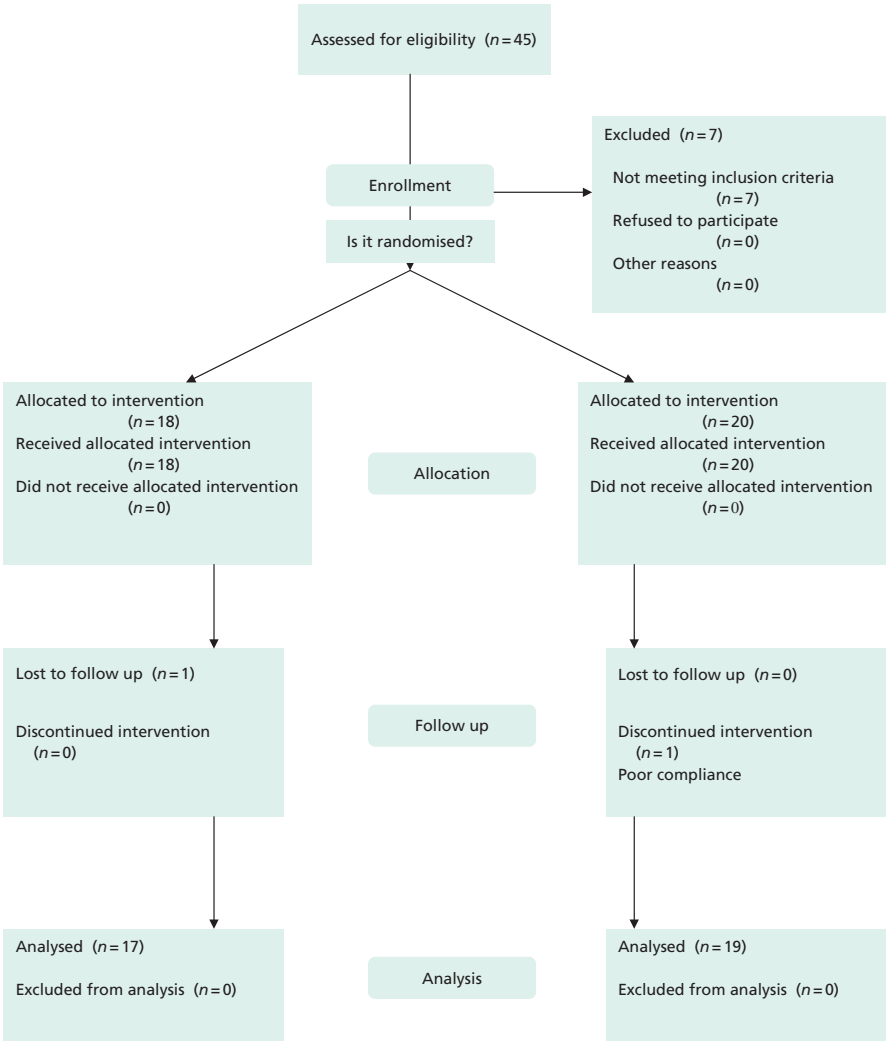


**Figure 1.** Flow chart of the study.

tablets identical in appearance, on a double-blind basis. Inosiplex dosage was 50 mg/kg daily for 12 weeks. The capsules were dispensed to the women by a third party. No other topical or systemic medication was administered during the study period. Subjects were advised to use condoms in order to avoid re-infection.

Response was evaluated by recording the number of lesions and by bi-dimensional measurements of the lesions, mapped on a schematic diagram of the cervix. The bi-dimensional measurements were expressed as a single parameter, which was the affected area in millimetres.[2] This study was performed at entry, every 4 weeks thereafter and at the end of therapy. Clinical evaluation was blinded to group assignment. Complete response was defined as the total clearance of cervical lesions; partial response was considered as a reduction of the affected area equal to or greater than 50%; no response was considered as less than 50% reduction in size. The reappearance of lesions after complete response was considered as relapse. Complete responders were followed up monthly for 12 months. Partial responders and nonresponders were administered other treatments.

Statistical analysis involved the $\chi^2$ test (Yates' correction included). The level of significance was fixed at $\alpha = 5\%$. To compare the demographic and clinical characteristics of the two groups, the $\chi^2$ test and the Mann–Whitney *U* test were applied.

Toxicity was monitored, on a monthly basis, both clinically and through laboratory tests, which included complete blood counts, renal and hepatic parameters and plasma uric acid levels. The protocol demanded treatment discontinuation in the event of significant toxicity.

## Results

Thirty-eight women aged 20–43 years (mean 27 ± 5 years) were enrolled during a 5-year period. The duration of lesions varied from 5 to 19 months. Of the women, 19 (47.5%) had involvement of both the external genitalia and the cervix. Previous conventional therapies for cervical genital warts included surgical excision and laser photocoagulation.

Group 1 consisted of 18 subjects, while group 2 included 20 subjects. Both groups were well matched for age, duration of infection, extent of involvement and previous therapies used. Thirty-six women were evaluable for response and toxicity. Two women were withdrawn from the study due to poor compliance or were lost to follow up. The flow chart of the study is presented in Figure 1.

The primary endpoint for evaluation of efficacy was at 12 weeks. The results are summarised in Table 1. The therapeutic difference (percentage of responders) between women receiving active and placebo therapy was statistically significant ($\chi^2 = 6.69$, $P < 0.01$). An intention-to-treat analysis was also performed. The therapeutic difference remained significant ($\chi^2 = 7.69$, $P < 0.01$) even when all 38 cases were considered.

At the secondary endpoint for evaluation of efficacy (completion of 12-month follow up), all complete responders remained in remission.

Inosiplex was generally well tolerated. The safety analysis included all 38 women. The adverse effects were mild and resolved upon completion of therapy. Two of the subjects who received active therapy complained of nausea (11.11%). Mild elevation of plasma uric acid levels were noted in four group 1 women (22.22%), which returned to normal a few weeks after the treatment was completed. No woman from both groups discontinued treatment due to adverse effects.

## Discussion

Our results seem to support the efficacy and safety of inosiplex as a systemic treatment for recalcitrant CA. Considering the potential of genital warts to resolve spontaneously in up to

**Table 1.** Participants' flow chart and efficacy at 12 weeks for oral inosiplex 50 mg/kg/day (group 1) versus placebo (group 2)

| | Group 1 | Group 2 |
|---|---|---|
| **No. of women who entered the trial** | 18 | 20 |
| **No. of women withdrawn (adverse effects or poor compliance)** | 0 | 1 |
| **No. of women lost to follow up** | 1 | 0 |
| **No. of evaluable women** | 17 | 19 |
| **Response** | | |
| Complete response | 4/17 (23.52%) | 0 (0%) |
| Partial response | 7/17 (41.17%) | 3/19 (15.78%) |
| No response | 6/17 (35.29%) | 16/19 (84.21%) |
| **Mean affected area ($mm^2$)** | | |
| Before treatment | 12.1 ± 5.1 | 12.9 ± 4.8 |
| After treatment | 5.7 ± 3.2 | 11.1 ± 4.6 |

20% of the cases, it cannot be ruled out that some of the responses were actually spontaneous remissions. However, this possibility seems less likely since the lesions of our women had been resistant to previous therapies, and the effectiveness of inosiplex was documented in comparison with placebo.

Previous experience suggests that inosiplex may improve efficacy when it is used as adjunct to conventional treatment for genital warts. Mohanty and Scott[4] treated 165 heterosexual men and women with genital warts either with inosiplex (1 g three times a day for 4 weeks) or conventional treatment, or both. They concluded that the use of inosiplex alone for treating genital warts is not justified. However, inosiplex was more effective in lesions of longer duration whereas conventional therapy in those of shorter duration. Davidson-Parker *et al.*[5] in a multicentre, prospective, randomised placebo-controlled study of 55 women with genital warts of at least 1-year duration documented that a 4-week course of inosiplex (3 g/day) improved the clinical response compared with conventional treatment. Like Mohanty and Scott,[4] they suggested that inosiplex may be worth considering as adjunct to conventional treatment for refractory genital warts. Sadoul and Beuret[6] found that the combined use of carbon dioxide laser and inosiplex reduced significantly the recurrence rate of CA.

In women with recurring and resistant CA, there is evidence of impairment of cell-mediated immunity. Indeed, it has been reported that in women with recalcitrant viral warts, the lesions disappeared at the same time the cell-mediated immunity response returned to normal.[7]

Inosiplex is a potentiator of both T lymphocyte and phagocytic cell function.[8,9] It also enhances the mitogen-dependent and antigen-dependent lymphocyte DNA synthesis.[10,11] It induces the appearance of phenotypic markers of differentiation on immature precursor T cells; augments helper or suppressor T cell functions and increases the production of lymphotoxin, a lymphokine.[12] The mechanism through which inosiplex exerts its beneficial effect in HPV infection is unknown. Regressing genital warts have been found to contain significantly more T lymphocytes and macrophages. CD4+ lymphocytes predominate both within the wart stroma and the surface epithelium, where there is a significant change in the CD4+/CD8+ ratio. The immunopotentiating activity of inosiplex has been shown to restore to normal the defective immunological cell-mediated response, and this may explain how the agent acts in the treatment of CA.[10]

In the present study, subjects were treated with daily dosage of oral inosiplex similar to that of previous experience but for a longer period of 12 weeks instead of the 4-week course used in the past. Oral inosiplex showed significantly increased efficacy compared with placebo in recalcitrant CA. It must be noted that the complete response rate (23.5%) was modest. However, if both partial and complete responders are considered, the actual percentage of successful treatment amounts to 64.7% and a statistically significant difference is documented between active and placebo therapy. The adverse effects noted were minor and no recurrences were experienced during the 12-month follow up. Considering the multifocal nature of HPV infection and its predilection for difficult-to-approach sites, systemic treatment with inosiplex seems to be an interesting and promising therapeutic alternative. ■

## References


1 Garland SM. Human papillomavirus update with a particular focus on cervical disease. *Pathology* 2002;34:213–24.

2 Armstrong DKB, Maw RD, Dinsmore WW, Blaakaer J, Correa MA, Falk L, *et al*. Combined therapy trial with interferon alpha-2a and ablative therapy in the treatment of anogenital warts. *Genitourin Med* 1996;72:103–7.

3 Campoli-Richards DM, Sorkin EM, Heel RC. Inosine pranobex. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986;32:383–424.

4 Mohanty KC, Scott CS. Immunotherapy of genital warts with inosine pranobex (Imunovir): preliminary study. *Genitourin Med* 1986;62: 352–5.

5 Davidson-Parker J, Dinsmore W, Khan MH, Hicks DA, Morris CA, Morris DF. Immunotherapy of genital warts with inosine pranobex and conventional treatment: double blind placebo controlled study. *Genitourin Med* 1988;64:383–6.

6 Sadoul G, Beuret T. Treatment of cervical and vulvar condylomata by $CO_2$ laser with an immunostimulant. *Rev Fr Gynecol Obstet* 1984; 79:681–4.

7 O'Neill BB, Robins DS. Isoprinosine in the treatment of genital warts. *Cancer Detect Prev* 1988;12:497–501.

8 Wybran J, Faman JP, Gortz R. Inosiplex (isoprinosine): a review of its immunological and clinical effects in disease. *Adv Pharmacol Ther* 1982;6:123–31.

9 Wybran J, Govaerts A, Appelboom T. Inosiplex a stimulating agent for normal human T cells and human leukocytes. *J Immunol* 1978;121: 1184–7.

10 Hadden JW, Hadden EM, Coffey RG. Isoprinosine augmentation of phytohemagglutinin-induced lymphocyte proliferation. *Infect Immun* 1976;13:382–7.

11 Ballet JJ, Morin A, Schmitt C, Agrapart M. Effect of isoprinosine on in vitro proliferative responses of human lymphocytes stimulated by antigen. *Int J Immunopharmacol* 1982;4:151–7.

12 Morin A, Ballet JJ. A recent review on in vitro and in vivo immunological activities of methisoprinol. *Allergol Immunopathol (Madr)* 1982; 10:109–14.