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Imiquimod for the treatment of genital warts: a quantitative systematic review

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Abstract

- Objective** To review published randomised controlled trials to assess the benefit and harm of imiquimod in the treatment of external genital warts.
- Data sources** MEDLINE (1966 – December 2000), Cochrane Library (Issue 3, 2000) and PubMed (December 15, 2000), review articles and reference lists.
- Review methods** Included studies had to be randomised trials of imiquimod, to be full published papers, and to have a comparison group. Quality of trial reporting was assessed. Relative benefit and number needed to treat were calculated for the main outcomes of wart clearance at the end of therapy, of at least 50% reduction in wart area, and of complete clearance at the end of treatment and no recurrence of warts during a follow-up period, as well as for adverse effect withdrawal or lack of efficacy withdrawal.
- Results** There were six trials, all with quality scores of 3 (out of 5) or greater. In five trials with HIV-negative patients complete clearance of warts at the end of treatment occurred in 51% of patients treated with imiquimod 2% or 5% cream and 6% of placebo treated patients. The number needed to treat was 2.2 (95% confidence interval 2.0 to 2.6). In four trials at least 50% wart area reduction occurred with 72% of patients treated with imiquimod 5% cream and 20% of placebo treated patients. The number needed to treat was 1.9 (1.7 to 2.2). In three trials complete clearance of warts at the end of treatment plus no recurrence occurred in 37% of patients treated with imiquimod 5% cream and 4% of those treated with placebo. The number needed to treat was 3.0 (2.5 to 3.8). Adverse event withdrawal was rare and no more likely with imiquimod than with placebo. Imiquimod was not effective in one trial in HIV-positive patients.
- Conclusion** The evidence base for imiquimod in treating genital warts is of high quality and the necessary size from which to draw useful conclusions. Imiquimod is effective in home application, though not in patients with HIV infection with the evidence presently available.

Introduction

External genital warts are common. In the UK in 1998 there were 111,000 reported new cases in clinics of genitourinary medicine [1]. Genital warts are the commonest sexually transmitted infection, affect mainly younger people, and usually caused by human papillomavirus genotypes 6 or 11. These genotypes are not normally involved with cancers. Association with human papillomavirus genotypes 16 and 18 can give rise to subclinical lesions associated with cervical intraepithelial neoplasia and squamous cancer.

A variety of methods have been used to treat external genital warts, and the primary goal of treatment before 1997 was the physical removal of symptomatic warts [2]. Methods used included excision, laser vaporisation, electrocautery, cryotherapy, caustic agents like trichloroacetic acid, podophyllin resin and intralesional interferon. Many of these are painful, which may result in undertreatment, whilst overtreatment can cause scarring or other complications. These treatments can also be expensive, as a number of outpatient visits may be required for a satisfactory result [2], and many have high rates of recurrence [2].

Guidelines for diagnosis and treatment have been published [3] and promulgated [4]. These guidelines are themselves based on earlier advice in the UK [5] and USA [6,7]. The involvement of primary care physicians in the treatment of genital warts is increasingly encouraged [4]. Choice of therapy depends on morphology of, and extent of the warts, as well as patient and professional choice, as outlined in a treatment algorithm used in Los Angeles [2]. Availability and cost may also be considerations. There are two choices for home treatment, imiquimod and podophyllotoxin gel [6].

This systematic review was performed in order to quantify the benefits and harms of imiquimod, and to provide fuller information upon which choice can be based. The intention was, where possible, to pool information on important clinical outcomes and to generate not only statistical significance between imiquimod and control, but also to provide measures of treatment efficacy, such as numbers needed to treat (NNT). NNT is treatment specific. It describes the *difference* between active treatment and control in achieving a particular clinical outcome [8]. Low NNTs indicate high treatment-specific efficacy. An NNT of 1 says that a favourable outcome occurs in every patient given the treatment but in no patient in a comparator group. This would be the 'perfect' result in, say, a therapeutic trial of an antibiotic compared with placebo with a sensitive organism. NNTs of 2 to 5 are indicative of high efficacy (as, for instance, with analgesics in acute pain [9]).

Imiquimod is a potent stimulator of cytokines, particularly interferons. A review of the mechanism of action of imiquimod is beyond the scope of this article, but there is an excellent account by Stanley [10].

Methods

QUORUM guidelines were followed [11]. Full journal publications of randomised trials of imiquimod in the treatment of genital warts were sought. Different search strategies were used to identify eligible reports from MEDLINE (1966 – December 2000), Cochrane Library (Issue 3, 2000) and PubMed (December 15, 2000). A series of free text searches were undertaken using the terms imiquimod, genital warts, anogenital warts, and condyloma acuminatum. Review articles [2, 10] were read for details of trials, and reference lists of retrieved reports were searched for additional trials. The manufacturers of Aldara (imiquimod 5% cream; 3M, Loughborough, Leicestershire, UK) were asked about clinical trials. Authors of papers were not contacted for unpublished reports or additional information from published reports. No restrictions to language were made.

Included were full publications of randomised trials that investigated imiquimod in the treatment of genital warts, and which had efficacy or safety data. Excluded were reviews with clinical information published in a fuller form elsewhere, studies with purely biochemical or immunological information, abstracts, or studies that used imiquimod for treating conditions other than genital warts.

Each report was scored for quality using a three item, 1-5 score, quality scale [12]. Points were awarded to studies according to whether they were randomised and double blind and mentioned withdrawals or drop-outs from the study. An additional point was awarded if both the method of randomisation and double blinding was described and was appropriate.

From each trial was extracted the number of patients treated per group, dosing regimes, study design, and the number of patients with efficacy and/or safety outcomes. RAM extracted the data into tables, and these were then read and checked by other authors. Prior definitions of outcomes of interest included those describing treatment efficacy (wart clearance) and those describing adverse events. For adverse events, treatment-related adverse event withdrawal has been shown to be the most commonly reported, and probably most useful measure [13], but the intention was also to combine information for particular local and systemic adverse events if reported in ways that allowed this. Three main efficacy outcomes and three harm outcomes were therefore sought from the trials, using the denominator of the number of patients randomised so that results were on an intention-to-treat basis. The main outcomes were:

- Complete clearance of warts present at the start of treatment.
- At least 50% reduction in wart area.
- Complete clearance of warts and no recurrence thereafter.
- Patients withdrawing from the study because of (reported) treatment-related adverse effects.
- Patients withdrawing from the study because of lack of efficacy.
- Patients with particular adverse effects.

There were additional minor outcomes of interest. One was the number of new warts that appeared after treatment started, and the clearance of these warts during treatment; clearly this could not be done on an intention-to-treat basis. Recurrence was also reported as the rate of recurrence in those patients with initial complete clearance. Again, this could not be analysed on an intention-to-treat basis.

Confidence intervals (95%) for single samples were calculated for proportions [14]. Relative benefit and relative risk estimates were calculated with 95% confidence intervals using a fixed effects model [15]. Heterogeneity tests were not used as they have previously been shown to be unhelpful [16]. Publication bias was not assessed using funnel plots as these tests have been shown to be unhelpful [17, 18]. The number needed to treat (NNT) and number needed to harm (NNH) with confidence intervals were calculated by the method of Cook and Sackett [19]. Relative benefit or risk was considered to be statistically significant when the 95% confidence interval did not include 1. NNT or NNH values were only calculated when the relative risk or benefit was statistically significant, and are reported with the 95% confidence interval. Statistical significance of any difference between numbers needed to treat for different doses or between men and women was assumed if there was no overlap of the confidence intervals, and additionally tested using the z statistic [20]. Calculations were performed using Microsoft Excel 98 on a Power Macintosh G4.

Results

A literature search found 16 reports for which full copies were obtained and read. Of these, 10 were excluded (Table 1) because they did not meet the inclusion criteria. A number of these were review or other articles with clinical information duplicated in other publications, but always with attribution. Where information on the same patients was available in duplicate reports, we used studies with the fullest amount of clinical information.

Details of the six included studies are given in Table 2. All six studies were conducted in the setting of home administration after initial professional examination and advice. Five of the studies were explicit that no other treatment was allowed within at least four weeks of the start of the trial. Wart location was predominantly vulvar or perianal in women, and penile or perianal in men. Five studies were conducted in North America or the UK using 5% or 1% imiquimod cream (Aldara, 3M Pharmaceuticals) [21-25], and

one [26] was conducted in Pakistan using a 2% cream manufactured locally. This latter study was included despite considerable lack of clarity about the formulation or nature of what was being applied (the title of the article indicated an imiquimod analogue was used), but with the prior intention of using sensitivity analysis with and without this trial. Four studies used application schedules of 6-10 hours overnight three times a week [21, 23-25], one for 24 hours three times a week [22], and the other (2% cream) applied twice a day for five consecutive days with a two-day rest period before repeat treatment. Duration of treatment was predominantly for 16 weeks (one study was 8 weeks with 24 hours duration for each application [22]), with a further follow up of 10 to 16 weeks to check for recurrence.

All the trials were described as randomised and double blind. No study described the randomisation process, and two disclosed that treatment and placebo were visually identical. All adequately described the number and reasons for withdrawals or dropouts from the trials. Quality scores were therefore 3 in four and 4 in two studies (Table 2) out of a maximum possible score of 5 and a minimum possible score of 1.

All the studies described the diagnostic procedures to diagnose genital warts. This was usually (four of five studies) a combination of clinical examination supplemented by biopsy and histology. One study used genetic techniques to identify HPV 6 and 11 [26]. In all studies but one wart area was assessed by inspection and mapping, and by photography, so that warts present initially could be identified and their area calculated and measured over time, and any new warts similarly identified and area measured [26].

The study populations were all adults. Five included men and women, though one had more than 90% men [22]. One study examined only women [26]. HIV seronegativity was a requirement in five studies, and the other examined only patients with HIV infection [24].

EFFICACY

Complete wart clearance

Pooling of data was considered for all the five studies with immunocompetent patients (and excluding the one study with HIV-infected patients [24]). Sensitivity analyses were performed by concentration of imiquimod, and by sex (using Beutner et al, 1998b [22] as data for men, who constituted over 90% of the population investigated). There was neither sufficient information (in terms of number of trials) nor difference in treatments (duration, intensity, and subsequent follow up for recurrence) to justify separate analyses.

Complete clearance of warts was reported in all five trials of HIV negative patients (Figure 1). This was achieved in 51% of patients (95% confidence interval 45% to 56%) treated with the highest concentration of imiquimod (2% in one trial, 5% in four), but in only 6% (3% to 8%) of patients treated with placebo cream. The NNT was 2.2 (95% confidence interval 2.0 to 2.6). This means that two patients have to be treated with 2% or 5% imiquimod for 8 to 16 weeks for one of them to have warts completely cleared (Table 3). The results for 5% imiquimod in four trials were similar. Substantially fewer patients were cured with 1% imiquimod in two trials, and for this concentration the NNT was 9.5 (5.9 to 25). In three trials results were more favourable for women (mean 72% clearance) than men (mean 37% clearance).

Imiquimod 5% cream was significantly more effective than imiquimod 1% cream for complete wart clearance (Table 3), with no overlap of confidence intervals of the NNTs ($z = 6.5, p < 0.001$). Imiquimod was more effective in women (72% of whom had complete wart clearance by the end of treatment) than in men (37%); there was no overlap of confidence intervals of the NNTs ($z = 4.2, p < 0.001$).

At least 50% reduction in wart area

This outcome was reported in four trials with imiquimod 5%, where 72% (67% to 78%) of patients had the outcome, compared with 20% (15% to 25%) with placebo. The NNT was 1.9 (1.7 to 2.2). This means that two patients have to be treated with 5% imiquimod for 8 to 16 weeks for one of them to have wart area reduced by at least 50% (Table 3). Substantially fewer patients were cured with 1% imiquimod in two

trials, and for this concentration the NNT was 8.1 (4.7 to 30). The number of trials and patients available for analysis by sex was small (Table 3), and results were more favourable for women (mean 85% with at least 50% reduction) than men (mean 68%).

Imiquimod 5% cream was significantly more effective than imiquimod 1% cream in producing at least 50% reduction in wart area (Table 3), with no overlap of confidence intervals of the NNTs ($z = 7.1$, $p < 0.001$). Imiquimod was more effective in women (85% of whom had at least a 50% reduction in wart area) than in men (37%); there was overlap of confidence intervals of the NNTs. There were too few trials to give confidence to this conclusion, however (Table 3).

Warts completely cured and not recurred

Because the object of treatment is clearance of warts without recurrence, this outcome was sought. Three trials with 5% imiquimod reported the number of patients randomised, the number completely cleared at the end of treatment, and the number of those who were completely clear at the end of treatment and in whom new warts were observed in the subsequent 10-16 weeks. Consequently the number of patients fulfilling this outcome could be calculated, with the number of patients randomised as the intention to treat denominator.

Warts were completely cured and did not recur in 37% (31% to 43%) of patients treated with imiquimod 5%, and 4% (2% to 6%) of patients treated with placebo. The NNT was 3.0 (2.5 to 3.8). This means that three patients have to be treated with 5% imiquimod for 8 to 16 weeks for one of them to have warts completely cleared, and for them not to recur (Table 3). Substantially fewer patients were cured with 1% imiquimod in two trials, and for this concentration the NNT was 10 (6.4 to 26).

Imiquimod 5% cream was significantly more effective than imiquimod 1% cream in ensuring that warts were completely cleared by the end of treatment and did not recur (Table 3), with no overlap of confidence intervals of the NNTs ($z = 5.2$, $p < 0.001$).

New warts

Three studies also reported on the number of new warts that appeared after the start of the study and before the end of treatment. New warts appeared in 30% (24% to 36%) of those treated with imiquimod 5%, 48% (41% to 55%) of those treated with imiquimod 1%, and 48% (42% to 55%) of those treated with placebo. The proportion of new warts appearing since the study started and which had completely cleared by the end was 39% (24% to 54%; 41 patients) with 5% imiquimod, was 21% (12% to 30%; 78 patients) with placebo, and the NNT was 5.4 (2.8 to 91) (Table 3). This means that for every five patients with new warts appearing after the trial started, one more had the new warts cleared by the end of treatment than with placebo.

Recurrence

Recurrence (defined as the number of patients with new warts when previously completely cleared) in the 10-16 weeks after the end of the treatment phase was reported in three trials. Recurrence occurred in 18/112 patients (16%; 95% confidence interval 9% to 23%) of those treated with imiquimod 5%, 2/30 (7%; 2% to 16%) of those treated with imiquimod 1%, and 1/13 (8%; -7% to 22%) of those treated with placebo. For the three large trials [21-23] 121/254 patients had warts cleared at the end of treatment with 5% imiquimod, and only 27/121 (22%) of these had a recurrence or reinfection.

ADVERSE EVENTS

In Table 4 details of how adverse events were measured are shown, together with adverse events and withdrawals. Most of the studies assessed local skin reactions at the site of cream application using patient and physician scales, though not all of the outcomes were reported uniformly.

Commonly reported adverse events were localised itching, erythema, burning and erosion or excoriation. The rates of moderate or severe adverse effects are given in Table 4. They were not pooled because it was not clear that the outcomes were the same, the numbers of patients included as the denominator was unclear, and information was not always given for imiquimod and placebo. Numbers needed to harm could not be calculated, nor could an overall weighted percentage of patients with moderate or severe reactions. Studies indicated that when local reactions caused problems, a temporary “holiday” from treatment reversed them, upon which treatment began again.

Withdrawals and the reason for withdrawals were clearly described. All causes of withdrawal were given, predominantly with assignment to treatment group. Treatment-related withdrawal (Table 4) included withdrawal because of adverse effects, and because of lack of effect. Adverse effect withdrawals were also given, so that withdrawal rates because of lack of effect could be calculated.

For adverse event withdrawal, there was no difference between placebo and imiquimod at all concentrations (relative risk 1.7; 95% confidence interval 0.4 to 9.9) or 5% cream (relative risk 1.9; 0.4 to 10, Table 5). Withdrawal because of lack of efficacy was described in five studies, and pooling information from the highest concentration of imiquimod in each trial (2% or 5%) showed that 1.7% (0.3% to 3.1%) of patients withdrew because of lack of effect with imiquimod, compared with 7.4% (4.3% to 11%) with placebo. The relative risk was 0.3 (0.1 to 0.7) and the NNH was -18 (-11 to -48). This means that for every 18 patients treated with imiquimod 2% or 5%, one fewer will discontinue treatment because of lack of effect than would have happened with placebo.

IMIQUIMOD IN HIV-INFECTED PATIENTS

The single study that was conducted in this setting [24] showed little benefit in terms of warts completely cleared (Table 2). The proportion with warts area reduced by at least 50% was 38%, significantly better than with placebo at 14% (Table 2). New wart appearance was similar. Adverse events (Table 3) were similar to non-HIV infected individuals, though one man had swelling and soreness of the prepuce and glans penis sufficient to necessitate circumcision.

Discussion

This quantitative systematic review demonstrates that imiquimod is effective in the self-treatment of genital warts at home, at the cost of some adverse effects associated with enhanced inflammatory reactions that were reversible when treatment was stopped temporarily. Studies were clinically homogeneous in terms of patient inclusion criteria and those who were excluded. For instance, the five studies used for data pooling all excluded patients with HIV infection. They were also homogeneous in terms of the treatment periods (8-16 weeks). Most used thrice-weekly applications though one [26] used daily application for five days with a two-day rest. In the latter case the maximum number of applications was 60, as compared to 48 in most others. The exception was a study that used a 24-hour application three times a week [22], but in that case the duration was only eight weeks. Maximum exposure to imiquimod was therefore similar.

A possible source of heterogeneity was the source of the imiquimod used in the trials. For five trials this was the formulation produced by 3M Pharmaceuticals, at 1% or 5% strength. One trial used a different strength (2%) [26], and unclear formulation. Sensitivity analysis therefore examined the highest concentration of imiquimod in all trials, that is data on 2% or 5% creams (Figure 1), and with 5% and 1% imiquimod creams separately.

Outcomes used to demonstrate efficacy were also homogeneous. These were patients with warts completely cleared, or with wart area reduced by half. Wart measurement was uniformly objective, with mapping and even with photographs to ensure objectivity. One outcome not reported, but one that could be inferred, was that of patients with warts completely cleared by the end of treatment, and with no recurrence of warts during the 10-16 weeks of follow up.

Numbers needed to treat for these outcomes were 2 (complete clearance or at least 50% reduction in wart area) or 3 (warts completely cleared by the end of treatment, and with no recurrence). This occurred despite very different absolute percentages of patients achieving the outcome, because placebo rates were high (20%) with the easiest outcome (at least 50% reduction in wart area) and as low as 4% with the hardest (warts completely cleared by the end of treatment, and with no recurrence). This is shown in Figure 2. Complete wart clearance by the end of treatment was 40-50% with 5% imiquimod (Figure 2, Table 3), with application three times a week. This is slightly less than the 62% clearance rate seen in a small non-randomised open study comparing this application strategy with daily application [27] published after searching had been completed.

There was a clear concentration-response, with 5% imiquimod consistently achieving higher clearance rates and lower NNTs than 1% (Table 3). Results for women were consistently better than for men for complete clearance, though not for at least 50% reduction in wart area (Table 3).

Recurrence of warts was described for patients in whom warts had cleared. The results of the pooled analysis tell us that about 50% of patients will have their warts cleared with 5% imiquimod, and that 40% will have warts cleared and there will be no recurrence. The implication is that for 4 out of 5 patients in whom warts clearance is achieved, no recurrence will occur. For the three large trials [21-23] 121/254 patients had warts cleared at the end of treatment with 5% imiquimod, and only 27/121 (22%) of these has a recurrence. It is unclear whether this recurrence rate of 22% can be compared with the higher recurrence rates (up to 95% with laser therapy) quoted for other treatments [7].

Adverse events were well recorded, especially withdrawal due to lack of effect and adverse events [13], and the methods used to collect adverse event information given in the five large trials (Table 4). Adverse events were actively sought at clinic visits in most studies, and diaries and prompts can lead to increased reporting of adverse events [28]. Local events related to enhancement of the inflammatory response, erythema, itching, burning, irritation and tenderness were common (Table 4), even at a moderate or severe intensity. Adverse events caused few patients to withdraw (about 2%), and this was not significantly different from placebo. Fewer patients given imiquimod withdrew because of lack of efficacy (Table 5).

The quality of the evidence was good on several counts. Not only was there clinical homogeneity, but the quality scores were 3 or 4, and scores of 3 or more have been shown [29, 30] to be associated with less likelihood of bias. Moreover for most of the efficacy outcomes there was enough data and a large enough effect to make it likely that the results would be free of any chance effects [31]. Efficacy was robust to sensitivity analysis, and there was a dose-response.

What the review cannot tell us is whether there are different patient groups (other than men and women) who might differentially benefit. For instance, there was no opportunity to perform an analysis based on the severity of the warts by number or area. That analysis could only be done using detailed information on individual patients. Nor was it possible to derive any information on the many practical issues that surround management of genital warts, such as personal hygiene, the ability to see the warts to adequately apply the treatments, unprotected sexual intercourse, clothing or other infections. Many of these practical problems may be beyond the scope of randomised trials, and therefore reviews of them.

The results of this systematic review complement guidelines for the diagnosis and treatment of genital warts in primary care [3, 4]. They demonstrate imiquimod to be effective in home application, though not in patients with HIV infection with the evidence presently available [24]. Rates of first attacks of genital warts have been rising for a decade [32], and an average primary care group of 100,000 population will have about 240 such cases a year, with as many again of recurrences and re-registered cases [32]. Pressures on hospital-led clinics, or their inaccessibility in rural areas, together with the availability of treatments like imiquimod that can be used at home, makes recognition of its role in primary care sensible [4].

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Competing interests

DH has received one lecture fee from 3M (paid into Trust Funds) in the past five years.

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FIGURE 1: WARTS CLEARED AT END OF TREATMENT WITH IMIQUIMOD 5% (YELLOW) OR 2% (RED). THE SIZE OF THE SYMBOL IS PROPORTIONAL TO THE SIZE OF THE STUDY.

FIGURE 2: PERCENTAGE OF PATIENTS WITH DIFFERENT OUTCOMES WITH PLACEBO (PINK) AND IMIQUIMOD (BLUE)

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Reviewers' reports

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Tanweer Syed

Comments to authors

The paper reads well but imparts some confusion for readership, such as:

The title says: 'Imiquimod for the treatment of genital warts: a quantitative systematic review' but many times the text advocates 5% cream "Formulation". This gives the idea that authors are endorsing or pushing 5% cream formulation to the readers because of the unrestricted grant received from 3M. Obviously there is only 5% imiquimod cream (ALDARA™) available by prescription and there is no such 1% or 2% imiquimod cream formulation in the market. So emphasis on the word 'formulation' should preferably be avoided. Same with the Discussion section, paragraph 2, sentence should be deleted because of unclear formulation (it draws readers' attention and causes confusion).

The objective of this systematic review was to quantify the 'benefits' and 'harms' of imiquimod. Is imiquimod harmful? Of course all drugs are harmful in some way but why mentioning it? I don't think any medical journal in Europe or North America will accept this word. In scientific writing, 'harm' has a big negative meaning to readership. It's better to use "adverse events or side effects".

In Results section, paragraph 2, sentence "The latter was included despite considerable lack of clarity about the formulation or the nature of what was being 'applied' " should be deleted. In all five studies mentioned in this manuscript, I couldn't see 'clarity of formulation', but writing this sentence in the manuscript give the idea that authors are biased or that it's the 'cream' and not the imiquimod which is eliminating genital warts. In fact, Reference 26 is the only study on genital warts with imiquimod which was not repeated, have used genetic techniques to identify HPV6 and 11 and not to mention, with no withdrawals.

Table 2, Syed et al.: under recurrence, "no data" is written, however, in the original paper, page 431, Table 1 showed 5 relapses (4 in imiquimod group and 1 in placebo) after 11 months.

Table 2, Syed et al.: under at least 50% reduction in wart area, "no data" is written. Could the authors please check the original paper page 432, under Results section, line 16: "reduction of 60% of target wart area to 1.8 mm²/lesion".

Jonathan Belsey

This is a well conducted quantitative systematic review that meets all the quality standards expected of this type of publication. It has been written up clearly and concisely and, assuming that the data presented in the accompanying spreadsheets are published as tables, there is sufficient data available for the analysis to be replicated, if required. The conclusions drawn are consistent with the data presented and will be of clear value to those responsible for initiating home treatment of genital warts.

There are two specific issues that I would like to see covered more fully in the final published version:

1. As imiquimod is considerably more expensive than the other currently licensed home treatment - podophyllotoxin - it will be important for prescribers to try to quantify the degree of additional benefit associated with imiquimod. It would therefore be useful to have a paragraph in the introduction giving some idea as to the efficacy/tolerability of podophyllotoxin or, if such studies do not exist, a statement to that effect.

2. In the statistical analysis a fixed effects model is used. This may well be justified but, as heterogeneity testing methods have now been somewhat discredited, it is difficult to be sure. As the number of studies involved was small, it may well be worthwhile reporting whether the wider confidence intervals one would expect with the use of a random effects model would have had any impact on the conclusions of the analysis.

Level of interest

A paper whose findings are important to those with closely related research interests

Advice on publication

Accept after revision, which I do not need to see

Quality of written English

Acceptable

Competing interests

Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this paper? If so, please specify.

I have received payments from Hayward Medical Communications in the past for the

writing of medical educational materials, although I have no current involvement with this company.

Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this paper? If so, please specify.

No

Do you have any other financial competing interests? If so, please specify.

No

Are there any non-financial competing interests you would like to declare in relation to this paper? If so, please specify.

No

24 April 2001

Response to referees' comments

Imiquimod for the treatment of genital warts: a quantitative systematic review

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'Imiquimod for the treatment of genital warts: a quantitative systematic review'

Response to reviewers

Jonathan Belsey

- 1 There is no systematic review of podophyllotoxin that we could find that could act as a basis for *relative* effectiveness or cost-effectiveness compared with imiquimod. We now state this in a final paragraph in the discussion.

As a general point, though, there are about 17 trials that *could* be included into a review of podophyllotoxin. One of the problems of reviews is where to draw the line on what to include in the overall scope. There is some sense in concentrating on one particular treatment, because the amount of work can get very large very quickly. There are exceptions to this, as for most things.

In any event, we were unable to find any systematic reviews of current treatments for genital warts. It would be a trifle unfair to penalise this one on imiquimod because no others have been done. So we agree with Jonathan, but cannot help.

- 2 For one outcome there was the bare possibility of a change in result by using a random effects rather than a fixed effects model. This is mentioned in the results section.

Tanweer Syed

- 1 We could find the word formulation three times in the manuscript (once in methods and twice in the discussion). The word formulation was chosen over strength because the title of Dr Syed's paper was that of an imiquimod *analogue*. This is nowhere defined in his paper, so formulation is the correct wording, while

strength is not. We cannot be sure that we were comparing like absolutely with like, but fortunately the pre-planned sensitivity analysis took care of this point so we did not have to belabour it.

Re-reading the manuscript for any evidence of bias through grammar or stress, we could find no suggestion that we were in any way "endorsing" or "pushing" the 5% formulation, though this is the only preparation that is commercially available. We are sure that Dr Syed in no way meant to imply that our work was influenced by the company: if he did, we would be very cross. If there is any specific point where the editors consider that there was evidence of undue bias or disproportionate emphasis in the manuscript, we would gladly address it.

2 The idea that treatments cause harm is commonly accepted.

3 We have redrafted this section and removed the word "considerable".

4 Dr Syed suggests that data from his paper could have been abstracted and used in the meta-analysis. We were looking for the number of patients with defined outcomes (and have amended the manuscript in methods and Table 2 to emphasis this point).

Unfortunately, the outcomes mentioned in the paper were not the outcomes we used. For instance, Table 1 of his paper does give "relapse at 11 months", but we have no information about the nature of relapse, or in which patients it occurred: it could mean patients with small wart areas later increasing in size, for instance. We *were* clear that we wanted patients with complete clearance of warts and no recurrence thereafter. Relapse is nowhere defined in the paper, and we could not be sure that the numbers referred to were what we wanted to abstract. Re-reading the paper confirms this. It may be argued (and, indeed, it may be) that that is the only possible definition of relapse, but unless that is stated we cannot be sure.

5 Again, we sought the number of patients with at least 50% reduction in wart area. That is not the same as a "reduction of 60% in target wart area to/lesion".

We do not wish to cause offense, but in the deliberately narrow definition of outcome we have chosen, there is no data, and Table 2 is correct.