

Imiquimod versus podophyllotoxin, with and without human papillomavirus vaccine, for anogenital warts: the HIPvac factorial RCT

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Scientific summary

The HIPvac factorial RCT

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Scientific summary

Background

Anogenital warts are the second most common sexually transmitted infection diagnosed in sexual health services in the UK; in 2017, there were 116,342 cases of genital warts treated in England. Over 80% of cases of genital warts are treated in sexual health services. Despite this, there is a lack of evidence to guide the choice of treatment. The two most commonly used treatments are self-administered topical agents podophyllotoxin and imiquimod, but these have never been compared in a large randomised controlled trial. The main alternative is cryotherapy, which may be combined with topical treatment. Recurrence of genital warts after any treatment is common, occurring in $\approx 30\%$ of cases. It is reported that treatment with imiquimod cream results in a lower rate of recurrence than podophyllotoxin.

Quadrivalent human papillomavirus vaccination has been used in the UK national vaccine programme for girls aged 12–13 years since 2012, and, more recently, in a targeted programme for men aged ≤ 45 years who have sex with men, and is now given to all boys aged 12–13 years. The vaccine is effective in preventing infection with human papillomavirus types 6 and 11, which cause 90% of genital warts, as well as human papillomavirus types 16 and 18, which cause 70% of cervical cancer. Whether or not the quadrivalent human papillomavirus vaccine has any therapeutic effect in wart clearance, or prevention of recurrence, is unknown.

Objectives

We aimed to compare the efficacy of imiquimod and podophyllotoxin creams in clearing anogenital warts by 16 weeks, and to establish whether or not the addition of the vaccine increases wart clearance. We also aimed to determine whether or not there was a difference in recurrence rate after using imiquimod or podophyllotoxin creams, and whether or not quadrivalent human papillomavirus vaccine reduces the recurrence rate after initial clearance in responders to imiquimod or podophyllotoxin when assessed 48 weeks after the start of treatment. Finally, we investigated the cost-effectiveness and cost utility of imiquimod and podophyllotoxin, both with and without the quadrivalent human papillomavirus vaccine.

Methods

Design

We conducted a randomised, controlled, multicentre, partially blinded factorial design trial. Participants were randomised equally into four groups: imiquimod plus quadrivalent human papillomavirus vaccine, podophyllotoxin plus quadrivalent human papillomavirus vaccine, imiquimod plus placebo, and podophyllotoxin plus placebo. Randomisation was stratified by gender, a history of previous warts and human immunodeficiency virus status. There was an accompanying economic evaluation.

Setting and participants

The study was conducted in 22 sexual health clinics in England and Wales. Participant inclusion criteria were patients aged ≥ 18 years presenting with new or recurrent anogenital warts. Exclusion criteria included treatment for warts in the previous 3 months, previous quadrivalent human papillomavirus vaccine, contraindications to any of the products (previous intolerance, pregnancy, lactation), a total wart area of $> 4 \text{ cm}^2$, patients requiring topical steroids applied to the affected area and patients on systemic immunosuppressive agents. Patients living with human immunodeficiency virus were initially excluded, but were included after a protocol amendment in December 2015. Written informed consent was obtained from all participants.

Interventions and follow-up

The topical treatments were used in accordance with the licence: 5% imiquimod cream (Aldara®; Meda Pharmaceuticals, Takeley, UK) applied three times per week for up to 16 weeks and 0.15% podophyllotoxin cream (Warticon®; GlaxoSmithKlein plc, Brentford, UK) applied twice daily for 3 consecutive days, with 4 days off, for 4 weeks. However, it is common practice to extend podophyllotoxin treatment for up to 16 weeks if a response is seen but warts persist, so this was permitted under the protocol. In addition, because slower responses may prompt a desire to switch treatment, cryotherapy was permitted after week 4 at the discretion of the local investigator, who also advised if dose modification was required in the event of local reactions.

The course of quadrivalent human papillomavirus vaccine (Gardasil®; Merck Sharp & Dohme Corp., Merck & Co., Inc., Whitehouse Station, NJ, USA) or saline control was started with initiation of topical treatment (with doses at 8 and 24 weeks). Participants were seen at randomisation and at weeks 4, 8, 16, 24 and 48.

Blinding

The topical treatment was unblinded as a result of the different posology. The vaccination was planned to be double-blind, but difficulties with sourcing and filling a matching placebo syringe led to a partially blinded design being adopted. The pre-filled syringes were presented in blinded packaging and the vaccine dose was administered by an unblinded member of the clinical team who was not involved in any study-related assessments.

Randomisation

Randomisation was carried out using minimisation with a random element, with gender, previous occurrence of warts and trial site as stratification factors. Human immunodeficiency virus status was added as a stratification factor when the entry criteria were changed. Participants were randomised 1:1 to either topical treatment and 1:1 to quadrivalent human papillomavirus or placebo. A secure online service (Sealed Envelope™; Sealed Envelope Ltd, London, UK) provided computer-generated participant identifiers and the trial arm allocations.

Outcome measures

The primary outcome was a combination of wart clearance at week 16 and remaining wart free at week 48. The two components of the primary end point were considered as factor-specific, clinically important secondary outcomes: for topical treatment, the proportion that were wart free at week 16; for vaccination, the proportion of those with wart clearance at week 16 and remaining wart free between week 16 and week 48. Additional secondary outcomes were specified, including the proportion that were wart free at the end of the assigned treatment course (4 or 16 weeks), the proportion that were wart free at week 16 without receiving additional treatment, the proportion that experienced complete wart clearance at any time up to week 48, adverse events, health-related quality of life and symptom scores.

The economic evaluation considered, as the base case, the incremental costs per quality-adjusted life-year gained by each intervention. In additional analyses, we used, separately, the components of the combined primary end point of the trial as the denominators in cost-effectiveness analysis, that is the incremental costs per additional patient clearing warts by week 16 and avoiding recurrence up to 48 weeks after starting treatment.

Sample size

The trial was originally designed with a sample size of 1000 participants. With 20% loss to follow-up, 800 participants would contribute primary outcome data. If the proportion achieving the primary end point in the less favourable topical treatment group was 35% (assuming a wart clearance rate of 50% and a 30% subsequent recurrence rate), this would have provided 80% power (at the 5% significance level) to detect an increase to 45% achieving the primary end point with the better treatment.

This corresponds to an odds ratio of 1.52. The same effect size would also have been detectable if vaccination reduced the recurrence rate from 30% to 10%, while leaving the wart clearance rate unchanged at 50%.

After failing to achieve the necessary recruitment rate, a revised sample size of 500 participants was agreed with the funder in February 2016. With 15% loss to follow-up, this would now provide only 52% power (at the 5% level) to detect the prespecified difference in the combined primary end point. However, it would still provide 80% power (at the 5% level) to evaluate each of the two components of the primary outcome: for the week 16 topical treatment outcome, a difference of 14% in wart clearance (57% wart clearance in the imiquimod group vs. 43% wart clearance in the podophyllotoxin group) could be detected, and, for the week 48 vaccine outcome, a difference of 16% in recurrence (12% recurrence in the vaccine group vs. 28% recurrence in the placebo group) could be detected. These differences were considered to be clinically important and sufficient to justify continuing the trial.

Protocol changes

In addition to the reduction in trial size, a number of other changes to the trial design were made. Withdrawal of pharmaceutical company support required a switch from a double-blind hepatitis A vaccine comparator group to a saline placebo and a partially blinded design. People living with human immunodeficiency virus were initially excluded, but the entry criteria were changed to allow enrolment of those stable on antiretroviral treatment or those with a normal cluster of differentiation 4 count.

Data collection and management

Data were centrally entered into a MACRO v4.0 (Elsevier, Amsterdam, the Netherlands) database with internal validation checks to improve data quality; data queries were resolved by site staff before database lock and final analysis.

Statistical methods

As detailed in the statistical analysis plan that was confirmed before the analyses were carried out, missing outcome data were imputed using multiple imputation with chained equations and the analyses for all primary and secondary outcomes were performed on multiply imputed data sets with results combined using Rubin's rules. The details of the variables included in the multiple imputation models and the number of imputations carried out are detailed in *Chapter 2*. All analysis models included gender, previous occurrence of warts, human immunodeficiency virus status and both treatment factors (topical treatment and vaccination) as covariates; trial site was included as a random effect. Adjusted treatment effect estimates, 95% confidence intervals and two-sided *p*-values were reported for each outcome measure.

All the analyses were conducted on a modified intention-to-treat basis such that all consented randomised participants for whom at least one follow-up visit was available were included in the analysis, regardless of their adherence to treatment. The HIPvac [Human papillomavirus infection: a randomised controlled trial of Imiquimod cream (5%) versus Podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts] trial was a pragmatic study concerned with the effectiveness and acceptability of both topical therapy and quadrivalent human papillomavirus vaccination.

The primary analyses for both factors (podophyllotoxin vs. imiquimod and quadrivalent human papillomavirus vaccine vs. placebo) were based on comparisons at the margins of the 2 × 2 table so that all participants randomised to podophyllotoxin were compared with all participants randomised to imiquimod and all participants randomised to quadrivalent human papillomavirus vaccine were compared with those randomised to placebo.

A substantial interaction between topical treatment and vaccination was not anticipated; results from a four-arm analysis (in which each of the four treatment groups were regarded as a separate treatment arm) are presented (see *Table 10*). A model including an interaction between the two factors was fitted as a secondary analysis.

Economic evaluation

The economic evaluation was conducted from the perspective of the NHS over the trial duration (i.e. without discounting future time preferences, because of a trial length of < 1 year). Apart from the characteristics outlined above, the economic evaluation explored a range of different aspects of the trial, including a comparison of quadrivalent human papillomavirus vaccine versus placebo and imiquimod versus podophyllotoxin; the difference over 16 weeks and 48 weeks; the difference between utility values mapped to the EuroQol-5 Dimensions, three-level version, and those obtained with the EuroQol-5 Dimensions, five-level version; the difference between three different study populations (the intention-to-treat population, the population that had never changed the allocated topical treatment and the complete-case population based on the utility scores); and the missing-at-random assumption for missing utility values. We also explored three different cost scenarios for the episodes of health-care visits in the absence of conclusive information and conducted a threshold analysis. The uncertainty associated with the imputation and the study sample was explored using a combined bootstrapping approach, and we calculated the probability of each treatment option being cost-effective based on the net monetary benefit, which can be defined as the difference in the value of monetised economic benefits (health outcomes and costs saved) in each arm, where the health outcome is expressed in monetary units, using a range of willingness-to-pay thresholds (£0–50,000 per quality-adjusted life-year).

Results

Baseline characteristics

Between November 2014 and January 2017, 506 participants were consented and randomised; 503 participants attended at least one follow-up visit. The mean age was 31 years, 66% of participants were male (24% were men who have sex with men), 50% of participants had a previous history of warts and 2% were known to be living with human immunodeficiency virus. The groups were well balanced at baseline.

Primary outcome

The primary outcome of the study was a combination of being free of warts at week 16 and remaining wart free at week 48 from the start of treatment. This was achieved in 35 out of 101 participants (35%) allocated to receive imiquimod and quadrivalent human papillomavirus vaccine, 38 out of 99 (38%) allocated to podophyllotoxin and quadrivalent human papillomavirus vaccine, 25 out of 98 (26%) allocated to imiquimod and placebo vaccine and 30 out of 99 (30%) allocated to podophyllotoxin and placebo. The denominator in each group is those participants who provided follow-up data at week 48.

For the primary outcome of wart free at week 16 and remaining wart free at week 48, the adjusted odds ratio for imiquimod relative to podophyllotoxin was 0.81 (95% confidence interval 0.54 to 1.23). This confidence interval provides no evidence of a difference between the topical treatments. Furthermore, the interval excludes a clinically meaningful treatment benefit of imiquimod over podophyllotoxin (odds ratio 1.52), but is consistent with a meaningful benefit of podophyllotoxin over imiquimod (odds ratio $1/1.52 = 0.66$). For the quadrivalent human papillomavirus vaccine versus placebo comparison, the adjusted odds ratio was 1.46 (95% confidence interval 0.97 to 2.20), so no effect has been shown. However, the lower boundary of the confidence interval was very close to 1, which suggests that the vaccine may improve the primary outcome, although this is inconclusive. Furthermore, this confidence interval includes an odds ratio of 1.52, which would have been a clinically meaningful effect of vaccine, as specified in the study design.

Secondary outcomes

The two components of the primary outcome were considered as important secondary outcomes, particularly given the reduced size of the trial. The first of these was the analysis of wart clearance at week 16: adjusted odds ratio 0.77 (95% confidence interval 0.52 to 1.14) for imiquimod versus

podophyllotoxin and adjusted odds ratio 1.30 (95% confidence interval 0.89 to 1.91) for quadrivalent human papillomavirus vaccine versus placebo. These differences were not significant but favour podophyllotoxin and vaccine. For remaining wart free at week 48 (in those who were wart free at week 16), the adjusted odds ratio of 0.98 (95% confidence interval 0.54 to 1.78) for imiquimod versus podophyllotoxin provides no evidence of a difference in recurrence rate between the two topical treatments. For the vaccine versus placebo comparison, there was an adjusted odds ratio of 1.39 (95% confidence interval 0.73 to 2.63). It is noted that the possible benefit of vaccine seen in the primary outcome analysis is a reflection of consistent effects seen in the two components.

Economic evaluation

The economic evaluation demonstrated that the costs and resource use were similar between the topical treatments, and there was a non-significant reduction in treatment costs with the quadrivalent human papillomavirus vaccine compared with placebo. The results were similar for both time frames. Patients had generally high health-related quality of life scores at baseline, with a clustering of responses on a few (very high) health states and overlapping confidence intervals. The values mapped on to the EuroQol-5 Dimensions, three-level version, were slightly lower than those obtained for the EuroQol-5 Dimensions, five-level version.

With the EuroQol-5 Dimensions, three-level version – the measure currently preferred by the National Institute for Health and Care Excellence – the treatment option with the highest ($\geq 50\%$) probability of being cost-effective was podophyllotoxin without quadrivalent human papillomavirus vaccine across the range of willingness-to-pay thresholds of £0–50,000 per quality-adjusted life-year, which increased to $> 75\%$ with the EuroQol-5 Dimensions, five-level version.

The incremental cost-effectiveness of adding the quadrivalent human papillomavirus vaccine to podophyllotoxin exceeded £80,000 per quality-adjusted life-year and thus cannot be considered cost-effective at the current list price of the vaccine at conventional willingness-to-pay thresholds. The factorial cost-effectiveness analysis gave negative incremental quality-adjusted life-years at higher incremental costs for the quadrivalent human papillomavirus vaccine. In addition, podophyllotoxin was always associated with positive incremental quality-adjusted life-years and fewer incremental costs than imiquimod (i.e. podophyllotoxin was cost-saving and dominated imiquimod). These findings were robust to different assumptions for imputing missing utility values.

The threshold analysis showed that adding quadrivalent human papillomavirus to podophyllotoxin could be considered cost-effective if the price of the quadrivalent human papillomavirus vaccine was substantially reduced below its list price, which is the case for the national human papillomavirus vaccine programme.

In the incremental analysis, the most cost-effective option per additional patient for clearing warts by week 16 and avoiding recurrence up to 48 weeks after starting treatment was, again, podophyllotoxin with placebo. Further health gains were achievable with podophyllotoxin and quadrivalent human papillomavirus at between £1280 and £1350 per additional patient remaining wart free by week 16. For the patients who avoided recurrence by week 48, further health gains were achievable with imiquimod plus placebo and imiquimod plus quadrivalent human papillomavirus (between £1400 and £2300 vs. between £2500 and £3000 per additional patient avoiding recurrence, respectively).

Conclusions

The trial had to be reduced in size from that originally proposed. A benefit of vaccine was not demonstrated in this trial. The odds of clearance at 16 weeks and remaining clear at 48 weeks were 46% higher with the vaccine, and consistent effects were seen for both the wart clearance and recurrence component outcomes, but these differences were not statistically significant. Imiquimod and podophyllotoxin had similar efficacy

in wart clearance, although the comparative confidence interval was wide. The trial results do not support earlier evidence of a lower recurrence rate with use of imiquimod compared with podophyllotoxin. The cost-utility analysis demonstrated that podophyllotoxin without quadrivalent human papillomavirus vaccine is likely to be the most cost-effective strategy at the current vaccine price, and adding quadrivalent human papillomavirus to podophyllotoxin may be cost-effective at a greatly reduced vaccine price.

Future work

Since this trial started, two randomised controlled trials of quadrivalent human papillomavirus vaccine versus placebo have been commenced to determine the effect on wart recurrence. There have been no further studies of the potential therapeutic effect; a trial larger than this one is required to definitively investigate this effect. Studies of the immune response in vaccine recipients with genital warts could elucidate a possible mechanism of action.

Trial registration

This trial is registered as ISRCTN32729817 and EudraCT 2013-002951-14.

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