Optimal frequency of imiquimod (Aldara) 5% cream for the treatment of external genital warts in immunocompetent adults: a meta-analysis
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CRD summary
The authors' conclusion that the optimal treatment regimen of imiquimod 5% cream for the treatment of external anogenital warts in immunocompetent adult patients is three times a week is reasonable.

Authors' objectives
To determine the optimal application of imiquimod (Aldara) 5% cream for the treatment of external anogenital warts in immunocompetent adult patients.

Searching
MEDLINE, Scopus and the Cochrane Library were searched to February 2007; search terms were reported.

Study selection
Randomised controlled trials (RCTs) of imiquimod 5% cream (three times a week or once daily dosing regimens) applied as a monotherapy at bedtime for 16 weeks in adults with external anogenital warts were selected. Eligible studies had to include the primary outcomes of the proportion of patients showing complete clearing of baseline warts by the end of the treatment period. Adverse effects were also reported, including the proportion of patients who withdrew from treatment and the proportion of patients who required at least one rest period from treatment. All studies used Aldara, 3 mol/L Pharmaceuticals with the same outcome measures to assess efficacy and safety. Studies included both men and women, men only (circumcised versus uncircumcised) or women only.

The authors do not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of double-blind placebo-controlled studies was assessed using the Jadad scale (5-point scale). A modified 3-point version of this scale was used to assess open-label studies. The authors do not state how many reviewers performed the quality assessment.

Data extraction
Effect sizes (aggregate proportions) were extracted from each study. Analysis of drug efficacy and safety outcomes was conducted on the intention-to-treat (ITT) basis. Data on patients who took at least one rest period from treatment due to adverse events were analysed on a per-protocol basis. Adverse events were categorised as severe (withdrawal from treatment) or moderate/mild (rest period from treatment required). Two reviewers extracted data from the primary studies.

Methods of synthesis
Studies were grouped according to three population subgroups (circumcised men, uncircumcised men and women) and pooled effect sizes (proportion showing complete clearance) with 95% confidence interval (CI) calculated using both fixed and random-effect models. Studies were weighted in inverse proportion to their variance. Statistical heterogeneity was assessed using the Χ² test. Differences between aggregate proportions for the different application frequencies or between patient subgroups were tested using the Z statistic.

Results of the review
Six studies were included in the review (n=974); four were phase II open-label studies and two were double-blind placebo-controlled trials. Both RTCs scored three on the Jadad scale. The quality scores of the open-label studies ranged from one to three.

Complete clearance rates ranged from 11% to 72% (circumcised men 11% to 42%; uncircumcised men 57% to 62%);
women 52% to 72%).

The effect size for circumcised men was 0.33 (95% CI: 0.24, 0.42) (2 studies, n=89) for three times a week treatment and 0.37 (95% CI: 0.26, 0.48) (2 studies, n=81) for once-daily treatment. The effect size for uncircumcised men was 0.62 (95% CI: 0.38, 0.86) (1 study, n=34) for three times a week treatment and 0.57 (95% CI: 0.39, 0.75) (1 study, n=30) for once-daily treatment regimen. The effect size for women was 0.59 (95% CI: 0.50, 0.68) (3 studies, n=103) for three times a week treatment and 0.67 (95% CI: 0.56, 0.78) (2 studies, n=74) for once-daily treatment. No evidence of significant statistical heterogeneity was found.

No difference in aggregate proportions of successfully treated patients was found in the different application regimens (three times a week or once daily) for circumcised men (z=0.11, p=0.9) and for women (z=0.38, p=0.7). No difference between treatment regimens was found in a single study of uncircumcised men (z=0.15, p=0.9). The effect size was higher in women than in circumcised men regardless of frequency of application (z=3.9, p=0.0001 three times a week; z= 4.2, p=0.0001 once daily). Imiquimod treatment was more effective in uncircumcised men than circumcised men, but only for three times a week application (z=3.3, p=0.001) compared with the once-daily regimen (z=1.93, p=0.054). Results from random effects model did not substantially affect the magnitude or direction of effect.

Withdrawal from treatment due to cutaneous reactions was similar for the two treatment regimens. The proportion of women and uncircumcised men who required a rest period from treatment was higher in the once-daily treatment regimen (z=2.4, p=0.02) than the three times a week regimen (z=2.7, p=0.007); no statistically significant difference was found in circumcised men.

**Authors' conclusions**
Application of imiquimod 5% cream three times a week is the optimal application schedule for external anogenital warts in immunocompetent adults, supporting current recommendations.

**CRD commentary**
The review question was supported by clear inclusion criteria. Three databases were searched for relevant studies and some attempts were made to locate unpublished material; there is a risk of language bias. Steps were taken to minimise reviewer error and bias in the data extraction, but the authors do not report if similar steps were used for study selection and assessment of study quality. The validity of the included studies was assessed and aggregate scores reported. The analysis appeared appropriate, though data sets were small and few direct comparisons between treatment regimes were available. Given the available evidence, the authors’ conclusion is reasonable, though more research may be useful.

**Implications of the review for practice and research**
Practice: These findings support current recommendations for scheduling imiquimod 5% cream treatment against genital warts.

Research: The authors indicate that patient skin type and duration of treatment course should be considered in future studies before changes in treatment are instituted.

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