

INPLASY PROTOCOL

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Imiquimod in cervical dysplasia: a review and meta-analysis

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Review question / Objective: To determine the efficacy of topical imiquimod in treatment of high-grade CIN (defined as regression CIN 1 or less), and to determine the clearance rate of high-risk human papillomavirus (hr-HPV), compared to surgical treatment and placebo.

Condition being studied: Women with an untreated, histologically proven, CIN2-3 lesion or women who were persistent high-risk HPV positive.

Eligibility criteria: Studies that evaluated the efficacy of imiquimod treatment in intraepithelial lesions or malignancy of other organs, and studies published as conference abstract, narrative review, editorial, letter, or short communication were excluded.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 November 2022 and was last updated on 14 March 2023 (registration number INPLASY2022110046).

INTRODUCTION

Review question / Objective: To determine the efficacy of topical imiquimod in treatment of high-grade CIN (defined as regression CIN 1 or less), and to determine the clearance rate of high-risk human

papillomavirus (hr-HPV), compared to surgical treatment and placebo.

Rationale: The current treatment for high grade CIN is LLETZ, but this treatment has potential side effect, also on future pregnancies. Our aim is to investigate a

non-surgical procedure to possibly avoid these side effects and to counsel women better about different treatment options for CIN.

Condition being studied: Women with an untreated, histologically proven, CIN2-3 lesion or women who were persistent high-risk HPV positive.

METHODS

Search strategy: This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist 16, the PRISMA –S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews 17, and meta-analysis of observational studies (MOOSE) checklist 18. The search was developed in Embase.com and then translated to other databases. The search was carried out on July 19th 2022 in the databases Embase.com, Medline ALL via Ovid and the Cochrane Central Register via Wiley. The search contained the terms imiquimod, cervical dysplasia and HPV (Table S1). No study registries were searched, but Cochrane Central retrieves the contents of ClinicalTrials.gov and the World Health Organization's International Clinical trials Registry Platform. No authors or subject experts were contacted, and we did not browse unindexed journals in the field. The search was repeated in february 2023.

Participant or population: Women with an untreated, histologically proven, CIN2-3 lesion or women who were persistent high-risk HPV positive.

Intervention: Imiquimod.

Comparator: LLETZ or placebo/no treatment.

Study designs to be included: Retrospective and prospective cohort studies as well as clinical trials that reported the efficacy of topical imiquimod in CIN2, CIN3 or persistent high-risk HPV infections.

Eligibility criteria: Studies that evaluated the efficacy of imiquimod treatment in intraepithelial lesions or malignancy of other organs, and studies published as conference abstract, narrative review, editorial, letter, or short communication were excluded.

Information sources: Embase.com, Medline ALL via Ovid and the Cochrane Central Register via Wiley. The reference lists of retrieved articles were searched for possibly missed relevant studies.

Main outcome(s): The efficacy of topical imiquimod in high-grade CIN lesions compared with LLETZ or placebo.

Additional outcome(s): The clearance rate of human HPV infection after topical imiquimod treatment, compared with LLETZ treatment, as well as to evaluate side effects associated with all treatment modalities.

Data management: All search were screened on title and abstract by two independent authors for relevance. The relevant articles were further assessed using the full text. In case of disagreement, the full articles will be discussed for further in or exclusion. Doubles were excluded.

Quality assessment / Risk of bias analysis: The methodological quality of the included studies was assessed with the Newcastle-Ottawa Quality Assessment Scale; the risk of bias with the Revised Cochrane risk-of-bias tools for randomized trials.

Strategy of data synthesis: Results were synthesized by performing random-effects meta-analyses to compute the weighted mean difference (WMD) for continuous variables and the pooled odd ratios (OR) for binary variables. All pooled estimations are displayed with their 95% confidence intervals (CI). The mean and standard deviation were calculated based on the method described by Wan et al. if not provided in the study²⁰. Existence of heterogeneity among study effect sizes was examined using the I² index and the Q-test p-value. An I² index > 75% indicated

medium to high heterogeneity. Categorical variables are presented as number (%), and continuous variables as mean \pm standard deviation (SD). Statistical significance was defined as a p-value < 0.05 . Publication bias was formally assessed using the Egger test. The analyses were performed using Review Manager (RevMan) version 5.4.1 (the Cochrane Collaboration, 2020).

AvdS, MK, AJK, FvK and HvB designed the study. AvdS and HvB collected the data. AvdS, MK and HvB analysed the data. AvdS, MK and HvB drafted the manuscript. All authors actively participated in interpreting the results and revising the paper and all authors approved the final manuscript.

Subgroup analysis: Not performed.

Sensitivity analysis: Not performed.

Language restriction: English and dutch.

Country(ies) involved: Netherlands.

Keywords: “Cervical intraepithelial neoplasia”, “human papilloma virus”, “uterine cervical dysplasia”, “LLETZ”, “treatment outcome “, “Imiquimod”, “squamous intraepithelial lesions”.

Dissemination plans: - present our study on an international congress - publish article in a scientific paper.

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