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SUMMARY WITH CRITICAL APPRAISAL

Imiquimod for the Treatment of Genital Warts: A Review of Clinical Effectiveness and Cost-Effectiveness

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Abbreviations

AE	adverse effects
AGW	anogenital warts
CDV	cidofovir
CI	confidence interval
CrI	credible interval
CTx	cryotherapy
GRADE	Grading of recommendations, assessment, development and evaluation
GW	genital warts
HIV	human immunodeficiency virus
MPV	human papilloma virus
IMQ	imiquimod
ITT	intention-to-treat
MTC	mixed treatment comparison
Mw	*Mycobacterium w*
NA	not applicable
NR	not reported
NS	not statistically significant
OR	odds ratio
PDP	podophyllin
PDT	podophyllotoxin
PLN	Polish Zloty (Polish currency)
QALY	quality adjusted life year
RR	risk ratio
TCCA	trichloroacetic acid
Tx	treatment

Context and Policy Issues

Genital warts (condylomata acuminate, venereal warts, and anogenital warts [AGW]) are lesions of the skin or mucous membrane caused by certain types of human papillomavirus (HPV).[1,2] Over 100 subtypes of HPV have been identified and of these about 30 subtypes infect the genital epithelium.[2] Approximately 90% of AGWs are caused by HPV subtypes 6 and 11.[2] AGW may occur as a single lesion or as multiple lesions, generally five to 15 lesions of 1mm to 10 mm in diameter.[2] Growth rates and spread of genital warts are variable, however accelerated growth may occur in pregnant or immunosuppressed individuals.[1] AGW may cause discomfort and distress and may negatively impact the individual's quality of life.[2,3]

The overall prevalence of AGW varies depending on the region considered as well as the methodology used for estimation. The prevalence estimated using retrospective administrative databases, medical chart review, or prospectively collected physician reports, ranged between 0.13% and 0.56%, while the estimates based on genital examinations ranged between 0.2% and 5.1%.[4] In Canada, the estimates of prevalence of AGW were 0.15% in British Columbia in 2006; and 0.15% in Manitoba in 2004.[4] Several treatment options are available for the management of AGW and include both surgical and non-surgical treatments. Surgical treatments include surgical excision, electrosurgery, cryotherapy, and laser surgery. Non-surgical treatments included various topical agents such as podophyllin (PDP), podophylotoxin (PDT), fluorouracil (FU), cidofovir (CDV), trichloroacetic acid (TCAA), and imiquimod (IMQ).[5] PDT blocks topoisomerase II activity and prevents cell division and thus inhibits the multiplication of AGW cells.[2] PDP contains PDT as an active metabolite.[2] FU reduces cell proliferation and induces cell death.[6] CDV disrupts elongation of the DNA chain and thus viral replication.[2] TCAA is a caustic agent which destroys cellular proteins and results in cell death.[2] It can damage healthy skin and is therefore not suitable for application by the patient.[2] IMQ is an immune-response modifier and leads to strong anti-viral and antitumor activity.[2,6] Treatments for AGW may be divided into two categories: provider-applied therapy or patient applied therapy.[5] Treatment with PDP, and TCAA may be provider applied, and treatments with PDT, FU, and IMQ may be patient-applied.[5] However, there appears to be some debate as to which treatments are optimal.

The purpose of this review is to compare the clinical effectiveness and cost-effectiveness of IMQ compared to other treatment modalities for the treatment of GW. This report is the third in the series of three reports on IMQ. The previous two reports were on IMQ for the treatment of basal cell and squamous carcinoma,[7] and actinic keratosis.[8]

Research Question

1. What is the clinical effectiveness of imiquimod for the treatment of genital warts?
2. What is the cost-effectiveness of imiquimod for the treatment of genital warts?

Key Findings

Evidence from systematic reviews with low quality included studies suggests that overall for patients with anogenital warts (AGW) compared to placebo, treatment with imiquimod (IMQ) is associated with statistically significantly greater clearance but statistically significantly greater adverse effects.

It appears that for patients with AGW, there were no statistically significant differences in clearance or adverse effects with IMQ compared with podophyllin, podophyllotoxin, cryotherapy, or *Mycobacterium w* vaccine. However, definitive conclusions were not possible due to the low quality of the studies, or the limited number of studies, or both.

Due to the uncertainty in the clinical effect, the cost-effectiveness of IMQ in the management of AGW is unclear.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology assessment agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. Conference abstracts were excluded from the search results. The search was also limited to English language documents published between January 1, 2012 and August 4, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients requiring treatment for genital warts
Intervention	Imiquimod (e.g., Aldara)
Comparator	Other active treatments or placebo
Outcomes	Clinical effectiveness, clinical benefits and harms, cost-effectiveness
Study Designs	Health technology assessments), systematic reviews, meta-analyses, randomized controlled trials (RCT), and economic valuations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Systematic reviews with all relevant studies included in a more comprehensive systematic review were excluded. Studies on patients with intraepithelial neoplasia were excluded. Studies on mixed populations comprising of patients with genital warts and patients with other conditions were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[9] randomized controlled trials (RCTs) were critically appraised using the Downs and Black checklist,[10] and economic studies were assessed using the Drummond checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 204 citations were identified in the literature search. Following screening of titles and abstracts, 195 citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, four publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. These comprised, one health technology assessment,[2] three systematic reviews,[5,12,13] and one randomized controlled trial.[14] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The study characteristics are summarized below and details are available in Appendix 2, Tables 2 to 4.

Health Technology Assessment, Systematic Reviews, and Randomized Controlled Trials

Study Design

One relevant health technology assessment[2] was identified. It included a systematic review of clinical effectiveness, which included 60 RCTs of which 14 RCTs on IMQ published between 1998 and 2011 were relevant for our report. In addition, it conducted a mixed treatment comparison analysis. Furthermore it included an economic evaluation which is discussed in the Economic study section below.

Three relevant systematic reviews[5,12,13] were identified. One systematic review[5] included 10 RCTs published between 1998 and 2011. One systematic review[12] had a broad objective (to assess CTx versus other treatments for AGW), and included 11 RCTs of which two RCTs published in 2008 and 2014 were relevant for our report. One systematic review[13] had a broad objective (to assess topical treatments for AGW) and included 18 RCTs of which eight RCTs published between 1998 and 2015 were relevant for our report.

One relevant double-blind RCT[14] was identified.

Country of Origin

The included health technology assessment[2] was published in 2016 from the UK. Of the three included systematic reviews,[5,12,13] one systematic review[12] was published in 2017 from France; one systematic review,[13] was published in 2017 from Germany; and one systematic review[5] was published in 2014 by the Cochrane Collaboration. The included RCT[14] was published in 2014 from India.

Patient Population

The included health technology assessment[2] included adult patients with AGW. The number of patients in the relevant individual studies ranged between 22 and 981. Reporting of age varied. Several studies reported minimum age > 18 years for eligibility; and for the studies that reported mean age, the mean age varied between 27 to 33 years. Eight studies included both females and males, two studies included only females, and four studies included only males.

All three systematic reviews[5,12,13] included non-immunocompromised adult patients. One systematic review[12] included a total of 204 patients; age and gender were not reported, however the eligibility criteria included patients older than 16 years. One systematic review included a total of 1734 patients; mean age ranged between 29 years and 33 years in eight studies, age range was 26 years to 35 years in one study, and one study did not report age; however, eligibility criteria included patients 18 years or older. In this systematic review[5] eight RCTs included both females and males, one study included only females and one study included only males. One systematic review[13] included a total of1223 patients; mean age ranged between 29 and 34 years and the proportion of females ranged between 0% and 50%.

The included RCT[14] included 89 patients, with 20% being female; the mean age was 29 years in the IMQ group and 26 years in the comparator group.

Interventions and Comparators

The health technology assessment[2] compared IMQ with placebo in pair-wise comparison. In addition, it included a mixed treatment comparison analysis including IMQ, PDP, PPT, TCAA, CDV, CTx, surgical methods, and placebo. In one systematic review[12] IMQ was compared with placebo. In one systematic review[5] IMQ was compared with placebo, PDP, PDT, or other provider-applied treatments. In one systematic review[13] IMQ was compared with placebo or PDT.

The included RCT[14] compared IMQ with *Mycobacterium w* (Mw) vaccine.

Outcomes

Outcomes included complete clearance,[2,5,13,14] clearance,[12] partial clearance,[5,14] recurrence,[2,5] and adverse effects[2,5,13,14] Complete clearance was generally defined as complete regression of the lesion. The definition of partial clearance was variable such as at least 75% clearance or at least 50% clearance of the lesions. The definition of recurrence was variable. In most studies, recurrence was defined as appearance of AGWs at a site previously cleared of AGWs, but some studies also included appearance of AGWs at sites additional to those initially cleared.

Economic study

The health technology assessment[2] described above also identified three economic studies on treatment with IMQ for patients with AGW, that reported on incremental cost-effectiveness ratio (ICER) values. All the studies compared IMQ with PDT. One study published in 2009 from Poland used a payer (patient and healthcare provider) perspective and a time horizon of 28 weeks. The second study published in 2003 from France used the perspective of the French national health insurance scheme and a time horizon of initial treatment of four to 16 weeks followed by three months follow-up. The third study published in 2003 from the UK, used the perspective of the UK national health services and a time horizon of 16 to 28 weeks. As the authors of the health technology assessment[2] did not identify any relevant economic studies that included health-related quality of life in the analysis, the authors conducted a cost-utility analysis incorporating health-related quality of life.

The cost-utility analysis used a payer perspective, and time horizon of 58 weeks. There was no discounting as the time frame was close to one year. Patients of 16 years or older with AGW were considered for the analysis. The interventions considered were no treatment, treatment with topical agents (IMQ, PDP, PDT, and TCAA) and ablative treatments (CO_2 laser therapy, CTx, and surgical excision). The economic model included a single episode of AGW rather than multiple episodes, first-line and second-line treatment, and considered complete clearance and recurrence. Cost inputs included cost of treatment and resources used. Costs of adverse events were not included. Cost-effectiveness was assessed in terms of benefit per quality-adjusted life year (QALY) gained and was presented mostly graphically. The probabilities of treatments to achieve the highest net benefit/QALY considering a willingness-to-pay threshold of £20,000 or £30,000 were presented.

Summary of Critical Appraisal

The critical appraisals of the studies are summarized below and details are presented in Appendix 3, Tables 5 to 7.

Health Technology Assessment, Systematic Reviews, and Randomized Controlled Trials

In the systematic review which was included in the health technology assessment report[2] and the three other systematic reviews[5,12,13] the objectives, and inclusion and exclusion criteria were stated, the study selection was described, and the list of included studies was presented. In all the systematic reviews[2,5,12,13] multiple databases were searched; in addition, in two systematic reviews[2,5] trial registries and reference lists of relevant articles were searched, in one systematic review[12] the reference lists of relevant articles were searched, and in one systematic review[13] a trial registry was searched. In three systematic reviews[2,5,13] the lists of excluded studies were provided and in one systematic review[12] the list of excluded studies was not provided. Article selection and data extraction were done independently by two reviewers in three systematic reviews[2,12,13] and by three independent reviewers in one systematic review.[5] Quality assessment was conducted in all the systematic reviews and the authors judged the majority of the included studies to have unclear risk of bias or high risk of bias. In all the systematic reviews[2,5,12,13] meta-analyses were conducted and one systematic review[2] also conducted a mixed treatment comparison analysis. In the systematic reviews, as there were few studies available for each outcome, exploration of publication bias was not considered to be feasible. In three systematic reviews[2,5,12] the authors declared that they had no conflicts of interest, and in one

systematic review[13] the authors had association with industry and the study was funded by a research grant from industry.

In the relevant RCT[14] identified, the objective, inclusion and exclusion criteria were stated, patient characteristics, interventions and outcomes were described. Details of randomization were not presented however treatments being compared were administered in a way such that they appeared to be indistinguishable. The study was appropriately blinded. Sample size calculation was conducted; however, the number of patients actually recruited was slightly less than predicted hence the study may not have had sufficient power to detect a significant difference between the treatments. Withdrawals in the two treatment groups were unequal and this could impact findings but the direction of impact is unclear. Intention-to treat analysis was undertaken. The authors mentioned that they had no conflicts of interest.

In the economic evaluation included in the health technology assessment report[2] the objective, strategies compared, time horizon, perspectives, and sources of clinical and cost data were stated. Indirect costs do not appear to have been considered. The evaluation was based on several assumptions however justification for the assumptions was provided and appeared to be reasonable. Incremental analysis was conducted and the probabilities of the treatments to have the best net benefit based on a particular willingness-to-pay threshold per additional QALY gained were presented. Sensitivity analyses were conducted and the results were generally robust. Conclusions were consistent with the results.

Summary of Findings

The study findings are summarized below and details are available in Appendix 4, Table 8.

What is the clinical effectiveness of imiquimod for the treatment of genital warts?

Clinical benefit

One health technology assessment[2] included a systematic review and a mixed treatment comparison analysis and showed that generally CO_2 laser therapy had higher probability of achieving complete clearance of AGW at the end of treatment compared to other treatments. At the end of treatment, the probability of achieving complete clearance with IMQ 5% cream was higher than placebo or PDT (0.3% cream), but lower than TCAA, PDP, PDT (0.5% cream, 0.3% solution), CTx, surgical excision, CO_2 laser therapy; however the credible intervals for the probabilities were large, indicating uncertainty in the findings. At six months or longer, the probability of recurrence with IMQ (5% cream) was higher than PDP (20% to 25%) or PDT (0.5% solution) but lower than surgical excision, however the credible intervals for the probabilities were large indicating uncertainty in the findings.

One systematic review[5] showed that compared with placebo, IMQ achieved statistically significantly greater complete clearance and partial clearance, but there were no statistically significant between group differences with respect to recurrence and appearance of new warts. It also showed that for IMQ compared with PDP or PDT, there were no statistically significant between group differences with respect to complete clearance, partial clearance, or recurrence.

One systematic review[13] showed that compared with placebo, IMQ (3.75% or 5%) achieved statistically significantly greater complete clearance but there was no statistically significant between group difference for IMQ (5%) compared with PDT (0.5%).

One systematic review[12] compared IMQ and CTx and showed that there was no statistically significant difference in clearance.

One RCT[14] compared IMQ (5%) with Mw vaccine and there appeared to be no difference in clearance between the two treatments.

Adverse effects

The included systematic review[2] with a mixed treatment comparison analysis showed that the risk of erythema with IMQ (5% cream) was statistically significantly higher compared with placebo but was not statistically significantly different compared with PDP (20% to 25%), or PDT (0.5% cream or solution). The risk of itching with IMQ (5% cream) was not statistically significantly different compared with placebo, PDP (20% to 25%), or PDT (0.5% solution). Both IMQ (5% cream) and PDP (20% to 25%) statistically significantly increased the risk of edema compared with placebo.

One systematic review[5] showed that compared with placebo, IMQ had statistically significantly greater local adverse reactions, but there were no statistically significant between group differences with respect to frequency of systemic adverse reactions. It also showed that for IMQ compared with PDP or PDT, there were no statistically significant between group differences with respect to local or systemic reactions.

One systematic review[13] showed that adverse effects were statistically significantly greater with IMQ (5%) compared with placebo but no statistically significant difference for IMQ (5%) compared to PDT (0.5%).

One RCT[14] compared IMQ (5%) with Mw vaccine and there appeared to be no difference in adverse effects between the two treatments.

What is the cost-effectiveness of imiquimod for the treatment of genital warts?

The included health technology assessment[2] reported incremental cost-effectiveness ratio (ICER) values from three economic studies on IMQ. One study reported an incremental cost of PLN 3865 per total clearing of warts for IMQ compared with PDT. The second study reported an incremental cost of €603 per patient cured at the end of treatment for IMQ compared to PDT. The third study reported an incremental cost of £2477 per sustained clearance for IMQ compared to PDT. The willingness-to-pay thresholds for these studies were not specified. Considering these findings, the authors of the health technology assessment[2] concluded that IMQ was associated with an incremental cost and an incremental benefit compared with PDT. As the authors of this health technology assessment[2] did not identify any relevant economic studies that included health related quality of life in the analysis, the authors conducted a cost-utility analysis incorporating health related quality of life.

The cost-utility analysis that was included in a health technology assessment report[2] compared various treatment strategies for AGW. It included IMQ 5% cream as one of the second line treatments in the economic model. It showed that at a willingness-to-pay threshold of £30,000 per QALY gained, the probability of a treatment resulting in the highest net benefit was 78% for the treatment strategy using 0.5% PDT solution followed by CO_2 laser therapy and 0.7% for the treatment strategy using 0.5% PDT solution followed by IMQ 5% cream. The authors mentioned that there was uncertainty around the cost-effectiveness of IMQ at second line as there was uncertainty in its clinical efficacy. The authors also

mentioned that PDT (0.5% solution) is an effective and relatively inexpensive treatment and is therefore likely to be prescribed as a cost-effective first-line treatment.

Limitations

Though the included systematic reviews were generally well conducted, they were limited by the low methodological quality of the included studies. Not all studies reported all outcomes.

There were few or no studies comparing IMQ with other available treatments for AGW, hence findings from indirect comparisons have been presented in the literature and need to be interpreted with caution.

There was overlap in the studies included in the systematic reviews hence findings are not exclusive.

The study settings were not always specified hence the generalizability to the Canadian setting is unclear.

As there was uncertainty around the efficacy of IMQ compared to other treatments, the cost-effectiveness of IMQ remains unclear.

Conclusions and Implications for Decision or Policy Making

One relevant health technology assessment,[2] three systematic reviews[5,12,13] and one relevant RCT[14] that compared IMQ with other treatments for patients with AGW were identified. The health technology assessment report[2] included a systematic review , a mixed treatment comparison analysis as well as an economic assessment.

It appears that for patients with AGW, compared to placebo, treatment with IMQ is associated with statistically significantly greater clearance but statistically significantly greater adverse effects. Though the evidence is from well conducted systematic reviews,[2,5,13] they are limited by the low methodological quality of the included studies.

It appears that for patients with AGW, there were no statistically significant differences in clearance or adverse effects with IMQ compared with PDT, PDP, CTx, or Mw vaccine. However, definitive conclusions are not possible due to the low quality of the studies, the limited number of studies, or both.

Studies comparing IMQ with other active treatments were few and for some active treatments no studies were available, so a mixed treatment analysis was included in the health technology assessment.[2] This analysis showed that the probability of achieving complete clearance with IMQ (5% cream) was 56% which was lower than the probabilities of clearance achieved with several other active treatments. However, the credible intervals were large, indicating considerable uncertainty in the findings. Due to the uncertainty in the clinical effect, the cost-effectiveness of IMQ for the management of AGW is unclear.

Findings need to be interpreted in the light of limitations.

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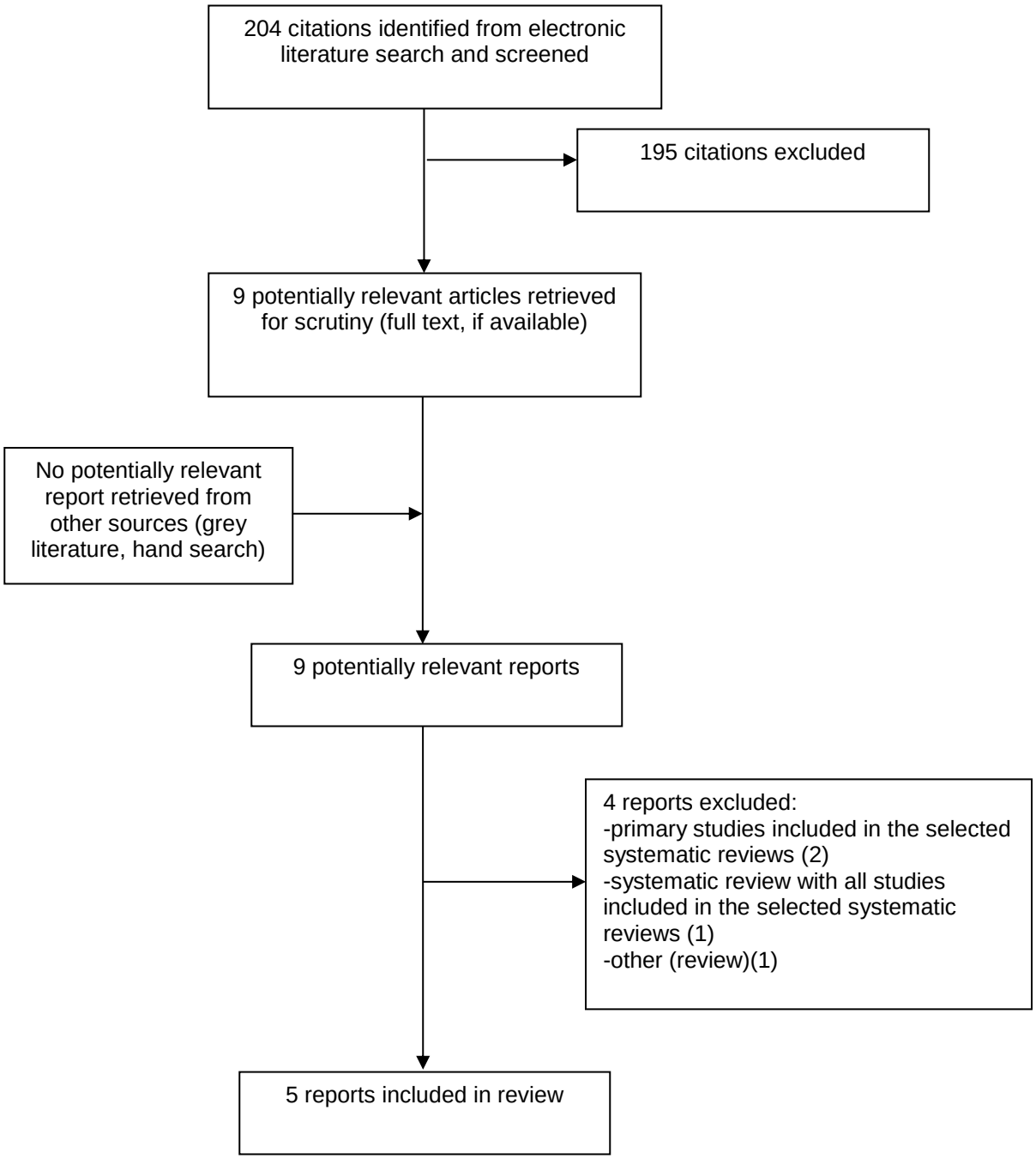
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, Year, Country	Type and Number of Primary Studies Included, Aim	Population Characteristics	Comparisons	Outcome
Health Technology Assessment				
Thurgar,[2] 2016, UK	This health technology assessment included meta-analysis, MTC analysis and economic analysis The systematic review of clinical evidence included 60 RCTs described in 70 reports published between 1981 and 2012. Of these reports, 14 reports included IMQ and were published between 1998 and 2011. Details of the economic evaluation are presented in Table 4. Aim: To conduct a systematic review to assess the clinical effectiveness of medical and surgical treatments for AGW and to develop an economic model to estimate the cost-effectiveness of treatments used in the UK	Patients with AGW N =2306 (the number of patients in the individual studies ranged between 22 and 981. Age: Reporting of age varied. Several studies reported minimum age > 18 years for eligibility; for the studies that reported mean age, the mean age varied between 27 to 33 years. Gender: 8 studies included both genders; 4 studies included males only, and 2 studies included females only.	Treatments assessed included: IMQ, PDP, PPT, TCAA, CDV, CTx, surgical excision, electrocautery, and placebo (Majority of the studies included PDP, followed next by IMQ). IMQ: 5% cream. PDP: PDP 20% to 25% (clinician applied); PDP (patient applied) PPT 0.015% cream or gel, 0.3% cream or solution, 0.5% cream or gel (patient applied). CDV: 1% cream.	Complete clearance recurrence, adverse events In most studies, recurrence was defined as appearance of AGWs at a site previously cleared of AGWs, but some studies also included appearance of AGWs at sites additional to those initially cleared
Systematic Review				
Bertolotti,[12] 2017, France	This systematic review included 11 RCTs of which 2 RCTs were relevant for our report. These 2 RCTs were published in 2008 and 2014	Non-immunocompromised, adult patients with AGW. N = 204 (120 in one RCT, and 84 in the other RCT) Age: NR % Female: NR	IMQ versus CTx. IMQ concentration was not reported	Clearance (specifics not presented)

Table 2: Characteristics of Included Systematic Reviews

Author, Year, Country	Type and Number of Primary Studies Included, Aim	Population Characteristics	Comparisons	Outcome
	Aim: To assess the efficacy and safety of cryotherapy with placebo or other agents for the treatment of AGW			
Grillo-Ardila,[5] 2014, Cochrane Collaboration	This systematic review 10 RCTs published between1998 and 2011; five RCTs from USA and one RCT each from Austria, Germany, Greece, India and Turkey. Aim: To assess the efficacy and safety of IMQ for the treatment of AGW	Non-immunocompromised, adult patients with AGW N = 1734 (the number of patients in the individual studies ranging between 22 and 534) Age: Mean age ranged between 29 years and 33 years for eight RCTs, age range was 26 years to 35 years in one study, and one study did not report age but had inclusion criteria of patients 18 years or older . Gender: Eight RCTs included both males and females, one RCT included only females and one study included only males. Prior history of treatment:: Seven RCTs included patients with a prior history of treatment, two RCTs included naïve patients, and one RCT did not report on prior history of treatment.	IMQ was compared with various other treatments. IMQ cream versus placebo (vehicle cream) (6 RCTs), IMQ cream versus patient applied PDT (1 RCT), IMQ cream versus patient applied PDP 20% (1 RCT), IMQ cream versus ablative methods (electrocautery, liquid nitrogen, laser therapy or surgical removal) (1RCT), IMQ cream versus CTx (1 RCT). 7 RCTs used IMQ 5%, 1 RCT used IMQ 2.5% or 3.75% and two RCTs used IMQ 1% Ablative methods and CTx were provider administered	Total clearance, partial clearance, recurrence, appearance of new warts, adverse effects. Total clearance was defined as complete regression of the lesion in all the RCTs. Partial clearance was defined as at least a 50% clearance of the lesions, in four RCTs; and at least a 75% clearance of the lesions, in two RCTs. Partial outcome was not reported in 4 RCTs.
Werner,[13] 2017, Germany	This systematic review included 18 RCTs of which 8 RCTs were relevant for our report. These 8 RCTs were published between 1998 and 2015 Aim: To assess the efficacy and safety of topical treatments for	Immunocompetent adult patients with AGW. N = 1223 (number of patients in the individual studies ranged between 20 and 322) Age (mean) in the individual studies ranged between 29 years and 34 years.	IMQ compared to placebo or PDT: IMQ (3.75% cream) versus placebo (2 RCTs), IMQ (5% cream) versus placebo (5 RCTs), IMQ (5% cream) versus PDT (o.5% solution) (1 RCT)	Complete clearance, adverse effects

Table 2: Characteristics of Included Systematic Reviews

Author, Year, Country	Type and Number of Primary Studies Included, Aim	Population Characteristics	Comparisons	Outcome
	AGW	% Female in the individual studies ranged between 0% and 50%		

AGW = anogenital warts; CDV = cidofovir; CTx = cryotherapy; IMQ = imiquimod; MTC = mixed treatment comparison; PDP = podophyllin; PPT =podophyllotoxin; RCT = randomized controlled trial; TCAA = trichloroacetic acid.

Table 3: Characteristics of Included Randomized Controlled Trial

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome, Follow-up
Kumar,[14] 2014, India	RCT; double-blinded (investigators, patients and the biostatistician were blinded). Setting: Department of dermatology and Venerology, All India Institute of Medical Sciences, India. Aim: To assess the efficacy and safety of Mw vaccine with IMQ (5%) cream in the treatment of AGW	Adult patients with AGW N = 89 (44 in IMQ group, and 45 in vaccine group) Age (mean): 29.4 years in IMQ group and 26.0 in vaccine group % Female: 20%	IMQ (5%) versus Mw vaccine. Patients applied IMQ (5%) or vehicle cream overnight, 3x per week for 16 weeks, irrespective of the clearance of warts. In addition patients received intradermal injection of Mw vaccine or vehicle every two weeks until complete clearance of AGW or for 16 weeks, whichever occurred first.	Complete clearance, partial clearance, adverse effects Follow-up: 3 months

Mw = Mycobacterium w; RCT = randomized controlled trial.

Table 4: Characteristics of Included Economic Studies

Author, Year, Country	Study Design	Perspective, Time Horizon, Currency, Discounting	Population	Interventions	Outcomes
Thurgar,[2] 2016, UK	This is the economic analysis section of the health technology assessment. Cost-effectiveness was determined by conducting a cost utility analysis. Model type: decision tree. Details of the clinical section and aim of this health technology assessment are described in Table 2.	Perspective: NHS (UK) and PSS; Time horizon: 58 weeks; Currency: £; Discounting: None (due to short time frame [about 1 year])	Patients of age 16 years or older with clinically diagnosed AGWs irrespective of biopsy confirmation.	The interventions considered in the analysis were no treatment, topical treatments (IMQ 5%, cream, PDP [20% to 25%], PDT 0.5% solution, and TCAA), ablative treatments (CO_2 laser therapy, CTx, surgical excision) and combination treatments ([CTx +PDP 25%], [CTx + PDT 0.15% cream], [TCAA+PDP 25%]). The interventions not considered in the economic analysis include: CDV, PDT 0.15% cream, electrotherapy, and any combination of treatments that are not listed among those considered. These were not considered due to lack of any supporting clinical data.	Cost effectiveness in terms of net benefit per QALY gained

AGW = anogenital warts; CDV = cidofovir; CTx = cryotherapy; IMQ = imiquimod; MTC = mixed treatment comparison; NHS = national health services; PDP = podophyllin; PDT =podophyllotoxin; PSS = personal social services; RCT = randomized controlled trial; TCAA = trichloroacetic acid.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR

Strengths	Limitations
Health Technology Assessment	
Thurgar,[2] 2016, UK	
Appraisal of the systematic review included in the health technology assessment: • The objective was clearly stated. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases (Medline, Embase, and Cochrane databases, Web of Science and NHS Economic evaluation databases) were searched from inception (or January 2000 for Web of science) to September 2014. Also, trial registries and reference lists of retrieved articles were searched. • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • List of excluded studies was provided • Article selection was done in duplicate • Data extraction was done in duplicate • Quality assessment was done in duplicate. Quality was assessed according to the recommendations of the Centre for Reviews and Dissemination and the Cochrane Handbook of Systematic reviews of Interventions and study quality was recorded using the Cochrane risk of bias tool. No study was judged to have an overall low risk of bias, with the largest number of studies having overall unclear risk of bias mainly due to limited reporting in the publications. • Characteristics of the studies were provided • Meta-analysis and mixed treatment comparison analysis were conducted • Low number of studies included in each meta-analysis precluded the assessment of publication bias • The authors mentioned that there were no conflicts of interest	• There appear to be no major limitations
Systematic Review	
Bertolotti,[12] 2017, France	
• The objective was clearly stated. • The inclusion criteria were stated. • The exclusion criteria were stated • Twelve databases were searched from inception to October 2016, but the databases searched were not specified. Reference lists of reviews were also searched. • Study selection was described • Flow chart of study selection was provided • List of included studies was provided	• List of excluded studies was not provided • Unclear if publication bias was explored. However considering the few included studies, investigation of publication bias using Funnel plots would not be feasible

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR

Strengths	Limitations
• Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was done independently by two reviewers using the Cochrane risk of bias tool. Also the quality of evidence was graded using the GRADE approach when there were ≥ 2 RCTs. Majority (all but one RCT) of the studies were considered to have high risk of bias • Characteristics of the studies were provided but details were lacking • Meta-analysis was conducted • The authors mentioned that there were no conflicts of interest	
Grillo-Ardila,[5] 2014, Cochrane Collaboration	
• The objective was clearly stated. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases were searched until April 2014 (Medline [from 1946], Embase [from 1947], LILACS [from 1982], Cochrane Sexually Transmitted Infections Group Specialized Register, Cochrane Central register of Controlled Trials [from 1991]. In addition trial registries, relevant websites and reference list of relevant publications were searched • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • List of excluded studies was provided • Article selection was done independently by three reviewers • Data extraction was done independently by three reviewers • Quality assessment was done independently by three reviewers using the Cochrane risk of bias tool. Also the quality of evidence was graded using the GRADE approach. No study was judged to have an overall low risk of bias, with most studies having overall unclear risk of bias or high risk of bias. • Characteristics of the individual studies were provided. • Meta-analyses were conducted • Publication bias was intended to be explored using Funnel plot and other tests but as there were fewer than 10 studies for each outcome, exploration of publication bias was not feasible • The authors mentioned that there were no conflicts of interest	• There appears to be no major limitations

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR

Strengths	Limitations
Werner,[13] 2017, Germany	
• The objective was clearly stated. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases from inception of database until March 2016 (Medline, Embase) and Cochrane Central register of Controlled Trials were searched. • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • List of excluded studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was done using the Cochrane risk of bias tool. Also the quality of evidence was graded using the GRADE approach. Majority of the studies had overall unclear risk of bias or high risk of bias. • Characteristics of the individual studies were provided. • Meta-analyses were conducted • Conflicts of interest were reported; the authors had industry association and the study was funded by a research grant from industry	• Unclear if publication bias was explored. However considering the few included studies, investigation of publication bias using Funnel plots would not be feasible

Table 6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black checklist

Strengths	Limitations
Kumar,[14] 2014, India	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was performed in blocks of six. Further details were not provided. Allocation was concealed. • Double-blinded study (patient, investigator, and biostatistician were blinded) • Sample size calculation was conducted. It indicated that 48 patients per group was required to detect a significant change, however the numbers in the two groups were slightly less: 44 and 45 in the IMQ and vaccine groups respectively. • Drop-outs (withdrew, lost to follow-up or defaulted) were reported; 7% in the IMQ group and 13% in the Mw vaccine group . • ITT analysis was done by carrying forward the last observation of the patient in case of missing data • *P*-values were reported but not always. • The authors mentioned that there was no conflict of interest	• Details of randomization were lacking • Sample size was less than that calculated to detect a significant change

IMQ = imiquimod, ITT intention-to-treat.

Table 7: Strengths and Limitations of Economic Studies using Drummond Checklist

Strengths	Limitations
Thurgar,[2] 2016, UK	
Appraisal of the economic analysis included in the health technology assessment: • Objectives were stated. • The strategies compared were stated. • Time horizon and perspective were stated. • Clinical data source were stated. Clinical data were from systematic review and MTC conducted. Clinical expert opinion was used for certain parameters such as duration of treatments, number of items per treatment period. Certain parameters such as duration of persistent warts, number of clinician visits, proportion of appointments with doctor and nurse were based on assumptions. • Cost data source were stated (obtained from the British National formulary, literature) • Incremental analysis was conducted and probabilities of the treatments to have the best net benefit based on a particular threshold of willingness-to-pay per additional QALY gained were presented. • Sensitivity analyses were conducted. • Conclusions were consistent with the results reported.	• Several assumptions were used, however they were described and justifications for the assumptions were presented. • Indirect costs do not appear to have been considered

MTC = mixed treatment comparison; QALY = quality adjusted life year.

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Health Technology Assessment</td></tr>
<tr><td colspan="2">Thurgar,[2] 2016, UK</td></tr>
<tr><td>
Patients with AGW

Clinical analysis
Probability of a treatment effect for achieving complete clearance at treatment end (from MTC analysis)
<table>
<tr><th rowspan="2">Treatment</th><th colspan="2">Mean probability (%) of being the best treatment</th><th>Probability (%) of complete clearance</th></tr>
<tr><th>Primary analysis</th><th>Sensitivity analysis[a]</th><th>Primary analysis</th></tr>
<tr><td>IMQ 5% cream</td><td>0.0</td><td>0.0</td><td>56.1</td></tr>
<tr><td>PDP (20% to 25%) (clinician applied)</td><td>0.0</td><td>0.0</td><td>62.1</td></tr>
<tr><td>Placebo or no Tx</td><td>0.0</td><td>0.0</td><td>7.6</td></tr>
<tr><td>PDT 0.5% gel (patient applied)</td><td>NA</td><td>0.5</td><td>NR</td></tr>
<tr><td>PDT 0.5% solution (patient applied)</td><td>3.8</td><td>0.0</td><td>92.6</td></tr>
<tr><td>PDT 0.3% solution (patient applied)</td><td>14.3</td><td>8.8</td><td>90.8</td></tr>
<tr><td>PDT 0.5% cream (patient applied)</td><td>0.0</td><td>0.0</td><td>73.7</td></tr>
<tr><td>PDT 0.3% cream (patient applied)</td><td>0.0</td><td>0.2</td><td>53.4</td></tr>
<tr><td>PDT 0.15% cream(patient applied)</td><td>NA</td><td>0.0</td><td></td></tr>
<tr><td>PDP solution (patient applied)</td><td>1.6</td><td>0.4</td><td>67.8</td></tr>
<tr><td>TCAA</td><td>0.0</td><td>0.0</td><td>61.4</td></tr>
<tr><td>CDV 1%</td><td>NA</td><td>5.6</td><td>NR</td></tr>
<tr><td>CTx</td><td>0.0</td><td>0.0</td><td>71.0</td></tr>
<tr><td>Surgical; excision</td><td>6.7</td><td>6.5</td><td>84.8</td></tr>
<tr><td>CO_2 laser therapy</td><td>71.8</td><td>62.1</td><td>97.1</td></tr>
<tr><td>Electrotherapy</td><td>NA</td><td>13.1</td><td>NR</td></tr>
<tr><td>TCAA +PDP 25%</td><td>0.0</td><td>0.0</td><td>72.8</td></tr>
<tr><td>CTx + PDT 0.15% cream</td><td>1.0</td><td>2.1</td><td>78.4</td></tr>
<tr><td>CTx + PDP 25%</td><td>0.0</td><td>0.5</td><td>77.6</td></tr>
<tr><td colspan="4">[a]Pre-specified sensitivity analysis included studies that (1) were judged to be at high risk of bias, (2) enrolled patients with AGWs who were seropositive for HIV infection, and (3) were reported only as conference abstracts.</td></tr>
</table>
Comparison of IMQ with placebo with respect to complete clearance (from standard pairwise meta-analysis)
<table>
<tr><th rowspan="2">Treatment</th><th colspan="2">OR (95% CI)</th></tr>
<tr><th>Primary analysis</th><th>Sensitivity analysis[a]</th></tr>
<tr><td>IMQ 5% versus placebo</td><td>13.48 (7.50 to 24.23)</td><td>10.02 (5.88 to 17.10)</td></tr>
<tr><td>PDT 0.3% solution versus placebo</td><td>81.00 (4.20 to 156.1)</td><td>NR</td></tr>
<tr><td colspan="3">[a]Pre-specified sensitivity analysis included studies that (1) were judged to be at high risk of bias, (2) enrolled patients with AGWs who were seropositive for HIV infection, and (3) were reported only as conference abstracts.</td></tr>
</table>
</td><td>
Clinical effectiveness:
"In summary, the evidence base to inform first-line treatment of AGWs, albeit large, is limited in terms of the number and quality of reporting of studies providing data on the effectiveness of individual interventions. Analyses indicate that ablative techniques, and in particular CO_2 laser therapy, are generally associated with higher probabilities of complete clearance at the end of treatment. Although topical treatments such as imiquimod 5% cream, podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream are the mainstay of patient-applied treatments, the evidence to support their use is limited, with analyses identifying considerable variation across topical treatments in the probability of achieving complete clearance." Page 140.

Cost-effectiveness:
"Cost-effectiveness finding 1. Podophyllotoxin 0.5% solution is an effective and relatively inexpensive treatment. It is therefore likely that prescription of this therapy first line would be considered a cost-effective use of resources.
Cost-effectiveness finding 2. No treatment and treatment with podophyllin are unlikely to be cost-effective treatment options for AGWs because of their relatively low rates of complete clearance and, in the case of podophyllin, higher estimated rates of recurrence, despite their low costs.
Cost-effectiveness finding 3. Highly effective treatments such as CO_2 laser therapy or surgical excision are likely to represent a cost-effective treatment option at second line following failure to completely clear with podophyllotoxin solution, provided that these treatments are considered clinically appropriate. This is because, despite their relatively high initial costs, these treatments are likely to
</td></tr>
</table>

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion

Comparison of IMQ with placebo or CO_2 laser therapy with respect to complete clearance (from MTC analysis)

Treatment	Complete clearance, OR (95% CrI)	
	Primary analysis	Sensitivity analysis[a]
IMQ 5% versus placebo	24.54 (7.28 to 73.04)	24.02 (6.68 to 64.44)
PDT 0.3% solution versus placebo	1008 (23.96 to 5253)	602.30 (21.46 to 3299)
CO_2 laser therapy versus placebo	6533 (65.49 to 25760)	4986 (64.22 to 28480)
IMQ 5% versus PDP 20% – 25%	1.07 (0.15 to 3.45)	1.09 (0.23 to 3.03)
PDT 0.3% solution versus versus PDP 20% – 25%	28.5 (0.97 to 143.4)	22.98 (0.99 to 122.10)
CO_2 laser therapy versus PDP 20% – 25%	104.6 (3.35 to 505.2)	171.20 (3.03 to 991.70)

[a]Pre-specified sensitivity analysis included studies that (1) were judged to be at high risk of bias, (2) enrolled patients with AGWs who were seropositive for HIV infection, and (3) were reported only as conference abstracts.

Recurrence at ≥ 6 months

Treatment	Probability (%) of recurrence (95% CrI)
IMQ 5% cream	24.7 (6.4 to 53.2)
Surgical excision	15.4 (4.7 to 33.5)
PDP 20% to 25%	55.9 (42.1 to 69.4)
PDT 0.5% solution (patient applied)	62.1 (37.6 to 82.7)

Appearance of new AGW during treatment

Treatment	New AGW, OR (95% CrI)
IMQ 5% cream versus placebo	0.57 (0.07 to 2.17), favors IMQ but NS
IMQ 5% cream versus PDT	8.70 (0.09 to 45.35), favors PDT but NS

Occurrence of erythema

Treatment	Erythema, OR (95% CrI)
Placebo versus IMQ 5% cream	0.15 (0.10to 0.24), favors placebo
PDP 20%-25% versus IMQ 5% cream	0.59 (0.19 to 1.40), favors PDP but NS
PDT 0.5% solution versus IMQ 5% cream	2.1 (0.29 to 7.87), favors IMQ but NS
PDT 0.5% cream versus IMQ 5% cream	0.91 (0.17 to 3.08), favors PDP but NS

Occurrence of edema

Treatment	Edema, OR (95% CrI)
Placebo versus IMQ 5% cream	0.05 (0.01to 0.13), favors placebo
PDP 20%-25% versus IMQ 5% cream	12.39 (2.74 to 40.21), favors IMQ

Occurrence of itching

Treatment	Itching, OR (95% CrI)
Placebo versus IMQ 5% cream	1.19 (0.03 to 6.0), favors IMQ but NS
PDT 0.5% solution versus IMQ 5% cream	18.0 (0.02 to 62.8), favors IMQ but NS
PDP 20%-25% versus IMQ 5% cream	6.8 (0.16 to 35.8), favors IMQ but NS

be effective and typically require only a single appointment with a clinician. Cost-effectiveness finding 4. There is uncertainty around the cost-effectiveness of treatment with imiquimod, TCAA and cryotherapy at second line. In this economic analysis, these treatments were not found to offer cost-effective alternatives at second line because of their relatively lower rates of complete clearance compared with CO_2 laser therapy and surgical excision. However, it is noted that the clinical systematic review reported uncertainty around treatment effects and rates of recurrence and, thus, clinical experience must be taken into account when using these treatments." Page 141

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion

Economic analysis

Probability of each treatment being considered as the treatment with the highest net benefit

Treatment	Probability (%) of the treatment resulting in the highest net benefit, based on a threshold of willingness-to- pay per QALY gained of	
	£20,000	£30,000
PDT 0.5% solution followed by CO_2 laser therapy	80.7	78.3
PDT 0.5% solution followed by surgical excision	15.9	15.1
PDT 0.5% solution followed by IMQ 5% cream	1.1	0.7
CO_2 laser therapy followed by surgical excision	0.6	3.0
PDT 0.5% solution followed by TCAA	0.5	0.5
PDT 0.5% solution followed by TCAA plus PDP 0.15% cream	0.4	0.4
Surgical excision followed by CTx plus PDT 0.15% solution	0.2	0.1
PDT 0.5% solution followed by CTx	0.1	0.0
PDT 0.5% solution followed by CTx plus PDP 25%	0.1	0.0
CO_2 laser therapy followed by CTx plus PDT 0.15% cream	0.1	0.3
CO_2 laser therapy followed by TCAA plus PDP 25%	0.1	0.1
Surgical excision followed by CO_2 laser therapy	0.1	1.2
CTx plus PDT 0.15% cream followed by surgical excision	0.1	0.1
CO_2 laser therapy followed by	0.0	0.2

Systematic Review

Bertolotti,[12] 2017, France

Non-immunocompromised adults with AGW

Comparison of CTx with IMQ

Outcome	Number of trials	Number of patients	RR (95% CI)	Hetero-geneity, I^2 (%)
Clearance	2	204	0.90 (0.73 to 1.12)	0

"*This systematic review with meta-analysis of cryotherapy efficacy and safety for patients with AGWs enabled us to conclude, with low-level quality of evidence, that no evidence supports cryotherapy superiority or inferiority when compared with TCA, imiquimod, or podophyllin and that cryotherapy appears slightly less effective than electrosurgery*." Page 523

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion

Grillo-Ardila,[5] 2014, Cochrane Collaboration

Non-immunocompromised adults with AGW

Comparison of IMQ with placebo

Outcome	Number of trials	Number of patients	RR (95% CI)	Hetero-geneity, I^2 (%)
Complete clearance[a]	6	1294	4.03 (2.03 to 7.99)	60
Partial clearance[a]	6	1082	2.56 (2.05 to 3.20)	0
Recurrence[b]	3	270	2.76 (0.70 to 10.91)	0
Appearance of new warts[c]	3	671	0.76 (0.58 to 1.00)	49
Pain[c]	2	804	11.84 (3.36 to 41.63)	0
Local reaction[c]	5	1225	1.73 (1.18 to 2.53)	73
Systemic reaction[c]	2	313	0.91 (0.63 to 1.32)	0

[a]After treatment
[b]During follow-up
[c]During treatment

Comparison of IMQ with other patient applied treatments (PDP or PDT)

Outcome	Number of trials	Number of patients	RR (95% CI)	Hetero-geneity, I^2 (%)
Complete clearance[a]	2	105	1.09 (0.80 to 1.48)	0
Partial clearance[a]	1	60	0.77 (0.40 to 1.47)	NA
Recurrence[b]	1	50	0.49 (0.21 to 1.11)	NA
Local reaction[c]	2	105	1.24 (1.00 to 1.54)	0
Systemic reaction[c]	1	60	0.30 (0.09 to 0.98)	NA

[a]After treatment
[b]During follow-up 0 to 6 months
[c]During treatment

Comparison of IMQ with other provider administered treatments

Outcome	Number of trials	Number of patients	RR (95% CI)	Hetero-geneity, I^2 (%)
Complete clearance[a]	2	335	0.84 (0.56 to 1.28)	84
Recurrence[b]	1	192	0.24 (0.10 to 0.56)	NA
Recurrence[c]	1	53	0.71(0.40 to 1.25)	NA
Pain[d]	1	80	0.30 (0.17 to 0.54)	NA
Local reaction[d]	1	80	0.55 (0.40 to 0.74)	NA

[a]After treatment
[b]During follow-up 0 to 6 months
[c]During follow-up 6 to 12 months
[dc]During treatment

"*The benefits and harms of imiquimod compared with placebo should be regarded with caution due to the risk of bias, imprecision and inconsistency for many of the outcomes we assessed in this Cochrane Review. The evidence for many of the outcomes that show imiquimod and patient-applied treatment (podophyllotoxin or podophyllin) confer similar benefits but fewer systematic reactions with the Imiquimod, is of low or very low quality. The quality of evidence for the outcomes assessing imiquimod and other provider administered treatment were of very low quality*." Page 2

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Werner,[13] 2017, Germany	
Immunocompetent adults with AGW Comparison of IMQ (3.75%) cream versus placebo Comparison of IMQ (5%) cream versus placebo Comparison of IMQ (5%) cream versus PDT (0.5%) solution	"*Our confidence in the pooled estimates ranged from very low to high. All investigated self-administered interventions for AGWs were superior to placebo with respect to CC. To determine the relative efficacy of the different self-administered interventions, head-to-head trials are needed*." Page 161 (CC = complete clearance)

Comparison of IMQ (3.75%) cream versus placebo

Outcome	Number of trials	Number of patients	Effect, RR (95% CI)	Quality, GRADE
Complete clearance	2	601	2.88 (1.94 to 4.51)	High
Drop-outs due to AE	2	601	2.14 (0.36 to 12.59)	Moderate
AE				
-Pain	1	NR	17.18 (1.04 to 282.95)	Low
-Erythema, inflammation, or skin irritation	1	NR	21.30 (1.30 to 348.79)	Moderate
-Erosion, excoriation, or ulceration	1	NR	13.45 (1.85 to 97.73)	High

Comparison of IMQ (5%) cream versus placebo

Outcome	Number of trials	Number of patients	Effect, RR (95% CI)	Quality, GRADE
Complete clearance	5	551	9.16 (3.39 to 24.71)	Low
Recurrence	3	NR	1.44 (0.28 to 6.97)	Low
Drop-outs due to AE	3	NR	4.3(0.48 to 38.34)	Moderate
AE				
-Pain	1	NR	16.00 (3.95 to 64.82)	High
-Erythema, inflammation, or skin irritation	3	NR	2.36 (1.87 to 2.98)	Moderate
-Erosion, excoriation, or ulceration	3	NR	6.80 (4.16 to 11.12)	Moderate

Comparison of IMQ (5%) cream versus PDT (0.5%) solution

Outcome	Number of trials	Number of patients	Effect, RR (95% CI)	Quality, GRADE
Complete clearance	1	51	0.87 (0.58 to 1.31)	Low
AE				
-Erythema, inflammation, or skin irritation	1	51	1.17 (0.8 to 1.73)	Low
-Erosion, excoriation, or ulceration	1	51	1.46 (0.42 to 5.00)	Low

Table 8: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Randomized controlled study</td></tr>
<tr><td colspan="2">Kumar,[14] 2014, India</td></tr>
<tr><td>Adult patients with AGW

Comparison of IMQ (5%) with Mw vaccine
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Effect, n (%)</th><th rowspan="2">P value</th></tr>
<tr><th>IMQ (5%), N = 44</th><th>Mw vaccine, N =45</th></tr>
<tr><td>Complete clearance</td><td>26 (59)</td><td>30 (67)</td><td>NR</td></tr>
<tr><td>Partial clearance (≥75% to < 100%)</td><td>9 (20)</td><td>7 (16)</td><td>0.52</td></tr>
<tr><td>Partial clearance (<75%)</td><td>9 (20)</td><td>8 (18)</td><td>NR</td></tr>
<tr><td>Adverse events</td><td></td><td></td><td>0.59</td></tr>
<tr><td>-Severe</td><td>6 (14)</td><td>4 (9)</td><td>NR</td></tr>
<tr><td>-Moderate</td><td>13 930)</td><td>9 (20)</td><td>NR</td></tr>
<tr><td>-Mild</td><td>22 (50)</td><td>27 (60)</td><td>NR</td></tr>
<tr><td>-None</td><td>3 (7)</td><td>5 (11)</td><td>NR</td></tr>
</table>
Viral load: The mean viral of HPV-6 significantly declined after treatment for both groups (P = 0.01 for IMQ (5%), and P = 0.003 for Mw vaccine</td><td>"Although it is invasive and associated with local immunologic reactions, intralesional Mw vaccine therapy is as effective as imiquimod, 5%, in the treatment of AGWs and results in elimination of HPV in the lesion." Page 1078</td></tr>
</table>

AE = adverse effects; CI = confidence interval; CrI = credible interval; CO_2 = carbon dioxide; CTx = cryotherapy; HIV = human immunodeficiency virus; HPV = human papilloma virus; IMQ = imiquimod, MTC = mixed treatment comparison; Mw = Mycobacterium w; NA = not applicable; NR = not reported; NS = not statistically significant; OR = odds ratio; PDP = podophyllin; PDT = podophyllotoxin; QALY = quality adjusted life year; RR = relative risk; Tx = treatment; TCAA = trichloroacetic acid.