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Complications and dosing frequency of 5% imiquimod for genital warts in a young man

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ABSTRACT A clinical decision report using:

Fife KH, Ferenczy A, Douglas JM Jr, et al. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. *Sex Transm Dis.* 2001;28(4):226-231. <https://doi.org/10.1097/00007435-200104000-00007>

for a patient with genital warts and an unstable social support network.

Keywords: *condyloma, warts, genital, men*

Clinical-Social Context

William Brown (pseudonym) is a 27-year-old man, who presented to the clinic for follow-up regarding adverse reactions to 5% imiquimod prescribed for peri-anal and penile condyloma acuminata. His reactions included flu-like symptoms, severe itching, ulceration, and burning, all of which began on the second week of treatment. These reactions led to a cessation of treatment for one week (3 doses), followed by two doses in one day, then daily application of imiquimod to “make up for missed times.” On resumption of imiquimod, he felt worsening burning and itching prompting his return visit. Mr. Brown has no significant past medical history or other sexually transmitted infections (STIs), which were tested for five weeks previously. This testing included HIV, syphilis, gonorrhea and chlamydia. The patient has had a total of four sexual partners, only one in the past year, all of which were male. He has always used barrier protection during intercourse except with his current partner who has no symptoms. On initial presentation, he had 3 peri-anal condylomas the largest measuring 10x7x3mm and one 3x2x2mm penile papule on his circumcised shaft. These were initially found by his partner and have been causing a great deal of distress for the patient as he had just stopped using protection due to being in a committed relationship. He cohabitates with his partner and his income was affected by the global pandemic. Mr. Brown is concerned that his partner will blame him for transmitting genital warts and that not having the condylomas treated will result in the end of his relationship and thus a loss of housing. Loss of affordable housing was particularly threatening because upon openly identifying as LGBT his family had “disowned” him. Consequently he has no social or financial support from his family and is concerned with the cost of other therapies. This stress led him to resume smoking 5 cigarettes a day after having quit for three years. It seemed as though his initial medical presentation was spiraling into a situation that could have serious long term adverse outcomes for his health.

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Clinical Question

Can 5% imiquimod be applied more frequently than the prescribed three times weekly to increase genital wart clearance in a gay man?

Research Article

Fife KH, Ferenczy A, Douglas JM Jr, et al. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. *Sex Transm Dis.* 2001;28(4):226-231. <https://doi.org/10.1097/00007435-200104000-00007>¹

Description of Related Literature

A search for original research was done on PubMed using the keywords “imiquimod”, “condyloma”, and “men”. The keyword “men” was included as males are known to have a difference in response to imiquimod treatment.² That search yielded 34 results. Thirty-one of those studies were rejected as they were not relevant to the clinical question for the following reasons; the most common reason for rejection was the study compared imiquimod to other treatments³⁻¹⁵, 5% imiquimod formulation was not being studied¹⁶⁻¹⁸, studied malignancies associated with HPV and not genital warts¹⁹⁻²³, studied specialty populations i.e. immunocompromised (due to HIV) or the persons’ genitalia was altered²⁴⁻²⁶, imiquimod being used as an adjunct post-procedural removal²⁷⁻²⁸, did not evaluate frequency²⁹⁻³¹, a study that was case reports³², or was a review of current guidelines³³.

Of the remaining three articles one was a meta-analysis.³⁴ This study’s reference list (30 articles) and cited by list (8 articles) were reviewed for other relevant studies. However, this only led to previously reviewed or irrelevant articles for the various reasons listed above. A study identified in the meta-analysis, also tested dosing frequency but focused solely on women.³⁵ This left 2 highly relevant studies, both of which were found by the above search and were evaluated in the meta-analysis.^{1,36} Both happened to be clinical trials that tested frequency of 5% imiquimod on genital warts. Gollnick et al. was a phase II, dose escalation, open-label, multicenter European study aimed at assessing safety.³⁶ However, it was not randomized, specified that the men must have a foreskin, and included HIV+ men. Mr. Brown would not have qualified for this study as he does not have enough wart burden on his penis and has no foreskin. Thus, the most suited study for critical appraisal was written by Fife et al.¹ The study closely approximated Mr. Brown’s clinical question by studying 4 different dosing frequencies of 5% imiquimod, 3 of which were greater than his prescribed dose. The area in question meets the criteria for SORT class B strength of recommendation given its consistent yet limited-quality patient-oriented evidence.³⁷

Critical Appraisal

This article describes a randomized control trial (RCT) that recruited participants from 9 clinical sites across the USA and Canada. The Strength of Recommendation Taxonomy (SORT)³⁷ classifies this study as having a level 2 study quality. It falls short of a level 1 ranking solely due to a suboptimal patient follow up rate below 80%. To be considered for this trial, men were required to have 2-50 condyloma acuminatum, confirmed by biopsy. Participants couldn’t have previously received imiquimod or had any other treatment 4 weeks prior to the study to constrain confounding variables. Predominantly HIV negative white males with an average age of 32 were studied, similar to the patient being described in this report making the study highly applicable. Upon enrollment patients were consecutively assigned a study number, which was placed on a randomization table, assigning each of the 110 patients to one of four treatment regimens. Regimens include applying 5% imiquimod either once (n=29), twice (n=29), three times daily (n=26) or the standard of care which is three times per week (n=26).

The selection criteria and successful randomization limit selection bias potential while providing a representative sample. Neither blinding nor placebos were utilized, likely due to ethical issues of post-marketing research with an already established drug efficacy, however patients were told about the doubt of the optimal regimen. The research being done after drug approval removes the possibility of publication bias. Additionally, the use of objective measures mitigates potential performance bias that could arise from a lack of blinding. Thus, no particular group appears to be favored. Measures were assessed at set intervals and included measuring

and photographing lesions and skin reactions such as redness, swelling, vesicles, erosions etc. Routine blood and urine tests were drawn to measure drugs levels, inflammation, and HPV antibodies.

Of the 110 participants, only 75 completed the study. 24 individuals were lost to follow-up, making it the most common attrition factor. 4 others withdrew due to adverse reactions to the treatment, the majority of which were in the most frequent dosing study arm. The low follow up rate is the reasoning behind this RCT receiving SORT level 2.37 This loss to follow-up is concerning as it leads to a large potential for bias in the results, which is not addressed in this study. It is unknown if the loss is due to adverse reactions, wart clearance or patient factors, such as patient embarrassment.

The primary outcome of the trial revealed that only 35 (31.8%) men showed complete wart clearance via intent to treat analysis. The percent clearance was different between treatment groups: 3x weekly (35%), daily (28%), twice daily (24%), thrice daily (27%), however was not statistically significant likely due to the small sample size. The clearance rates are likely artificially reduced due to the analysis including the 32% lost being treated as failures. Nonetheless, the median percent reduction of wart area was over 90% in all groups with the greatest reduction being seen in the 3x weekly frequency arm. Again, this was not statistically significant. Of note, 39 participants developed new lesions during the 16-week trial and 15 men cleared these new lesions. Interestingly, though more frequent dosing decreased the incidence of new lesions, a decrease in clearance was associated with increased frequency. This unexpected finding, although not statistically significant, was hypothesized to be due either to intermittent drug free periods from adverse medication reactions in more frequent dosing schedules or cytokine hyperresponsiveness due to repeated stimulation.

Safety was assessed by reported adverse events (erythema, vesicles, ulcerations, excoriations, pain and systemic symptoms). Fortunately, these symptoms do not overlap with symptoms of condyloma, alleviating ascertainment bias. These adverse reactions were assessed by clinicians at each visit by comparing photographs, which occurred after weekly for the first month followed by every other week for the following 3 months. Additionally, patients kept diaries of self-reported events and compliance that were reviewed at each visit. There was a non-significant increase in the number of adverse events with increasing frequency of imiquimod, but a significant increase in the severity of the events. The 58.3% rate of adverse events in the standard treatment compared to 76.9% in the thrice daily. The number needed to harm (NNH), when compared to the treatment standard of 3x per week, is a key statistic not included in this study; daily (NNH=26.3), twice daily (NNH=6.33), thrice daily (NNH=5.38). Unfortunately, this statistic does not reflect the increased severity of the reactions. Adverse reaction severity also led to an associated increase in rest periods or a period of missing doses to allow for reactions to subside. Of those in the 3x weekly group, 9 took a rest period, compared to 18 in the daily group, 24 in the twice daily, and 20 in the thrice daily group. Oddly, systemic adverse events were not associated with dosing frequency. Upon investigation of adverse reactions, no meaningful abnormalities in chemistry or hematologic values were noted, nor was imiquimod detected in patients' serum.

Generally, the study was able to answer that optimal dosing frequency is three times weekly, however it was not statistically significant. This limitation is likely due to the small sample size as well as the low follow up. Of greatest concern is the potential for source bias, as funding for this study was provided by 3M Pharmaceuticals, the producer of Aldara-brand imiquimod. Whether this affected the study is unknown.

Clinical Application

Mr. Brown would have met criteria to be screened for inclusion of the study by Fife et al. as he is a male with more than 2 condylomas with an area greater than 30mm², supporting strong external validity. Regarding whether 5% imiquimod can be applied more frequently than 3 times weekly to accelerate wart clearance, the study indicated not. In fact, increasing dosing is associated with an increase in the number and severity of reaction as well as increasing the number of rest periods. This study can be applied to Mr. Brown's case as it showed a range of different application frequencies as well as the effects of these frequencies, mirroring Mr. Brown's situation. While this information was not statistically significant it has been reproduced in other non-randomized trials and also showed a nonsignificant decline in efficacy with increased frequency.^{9,36} Thus, it was recommended that he use the imiquimod as prescribed.

To address the Mr. Brown's concerns regarding limited funds, imiquimod was recommended. Imiquimod is the cheapest patient-applied option according to GoodRX, for peri-anal warts. Additionally, the increase in stress, both



financial and personal, has led to his resumption of smoking, which can be expected based on previous studies.³⁸ It has been shown that this elevated stress increases disease burden of HPV³⁹, and that the resultant smoking decreases wart clearance in men.⁴⁰ These factors were discussed with the patient and a referral was placed to a mental health provider to improve coping skills. Mr. Brown acknowledged his need to quit smoking as well as his understanding that imiquimod is best applied 3x weekly for best overall results. While not statistically significant, there were no harms in providing this information as no difference were seen in clearance with differing frequencies. There is strong internal validity to this study as the results match the conclusion. The possible benefits are a reduction in the number of adverse reactions and an almost certain decrease in the severity of his reactions, which will likely decrease his stress surrounding the matter.

New Knowledge Related to Clinical Decision Science

Although there are no randomized clinical trials large enough to provide statistically significant evidence on the frequency of 5% imiquimod dosing, this study provides notable associations surrounding the negatives of his increased dosing frequency secondary to an adverse reaction. The increased reaction severity and possible decrease in efficacy associated with increased dosing were discussed with Mr. Brown as well as the limitation of this study. Information such as this is essential to many patients, especially in times of stress when a disease could alter lives in ways clinicians cannot initially foresee.

The lack of information and heightened stress led to behavior that might have worsened the patient's medical response, which in turn created an adverse reaction, further increasing stress. This stress, compounded on existing stress provoked Mr. Brown to resume smoking, entailing a cadre of associated diseases. While information can help the patient, it is necessary that providers review articles thoroughly to utilize the most appropriate study and interpret the information as the analysis done can alter the conclusion taken from the data. Always keep in mind the various biases that can affect one's results and interpretation.

Ultimately, Mr. Brown needed advice on the dosing of imiquimod, which was available in the clinical research literature. But, this evidence is nested within a vast set of other needs, most of them social and emotional. Clinical Decision Science requires that the clinical evidence harmonize with other aspects of this therapeutic relationship. Because of the non-supportive nature of his relationships with his family and domestic partner, it is even more important that the doctor patient relationship model respect and care. A simple way to do that is to ask for a short interval follow up visit to re-assess the response to therapy and verify success of referral advice in a health system struggling with a pandemic.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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