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ORIGINAL ARTICLES

Efficacy of topical imiquimod in HIV-positive patients with recurrent anal condylomata acuminata

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ABSTRACT: **Introduction**: Imiquimod is a topical chemotherapic and immunostimulant agent with antitumoral and antiviral activities, used for anal condylomata acuminata treatment, mainly in recurrences. **Objective**: Evaluate the imiquimod efficiency in chronic and recurrent anal condylomata acuminata in HIV-infected persons. **Method**: A prospective study that analyzed 61 patients with recurrent anal condylomata treated with topic 5% imiquimod, for at least 8 weeks. These patients had already been submitted to other topical and surgical treatments for anal warts. We evaluated the efficiency of this agent, through wart remission, with clinical examination and high-resolution anoscopy, $CD4^+$ T lymphocyte count and side effects. The patients were 55 males and 6 females, from 22 to 63 years old. **Results**: Remission was seen in 90%, being 46% complete remission and 44% partial remission. Other 10% did not respond to the treatment with imiquimod within the 16^{th} week. Recurrences were observed in 11% of patients in 24-week follow-up. Statistics showed no differences in $CD4^+$ T cell scores when groups with and without complete remission were compared. Adverse effects were reported by 45% of patients. They were mild to moderate burning (25%), intense burning (7%), ulcerative dermatitis (8%) and systemic symptoms (5%). **Conclusion**: Imiquimod was effective in controlling recurrent anal condylomata acuminata in HIV-positive patients, regardless of $CD4^+$ T cell count.

Keywords: papillomavirus infections; condylomata acuminata; immunotherapy.

RESUMO: **Introdução**: O imiquimode é agente tópico quimioterápico e imunoestimulante, com atividades antitumoral e antiviral, usado para tratamento dos condilomas acuminados perianais, principalmente os recidivantes. **Objetivo**: Avaliar a eficácia do imiquimode nos condilomas acuminados perianais crônicos e multirrecidivantes dos doentes soropositivos para o vírus da imunodeficiência adquirida (HIV). **Casuística e Método**: Estudo clínico prospectivo por 12 meses em que observamos o uso tópico de imiquimode creme 5%, por no mínimo 8 semanas, em 61 portadores de condilomas acuminados perianais recidivantes e de difícil controle, e que já haviam sido submetidos a vários outros tratamentos clínicos e operatórios. Avaliamos a eficácia do produto quanto sua remissão (através de exame clínico e colposcópico), nível dos linfócitos T $CD4^+$ e efeitos adversos. Foram 55 homens e 6 mulheres com idade entre 22 e 63 anos. **Resultados**: Obtivemos 90% de remissão, sendo 46% de resposta completa, 44% de resposta parcial e 10% sem qualquer resposta em até 16 semanas de tratamento com imiquimode. A taxa de recidiva atingiu 11% em 24 semanas de seguimento. Quanto ao nível de linfócitos T $CD4^+$, não

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observamos diferença estatística entre o grupo que atingiu remissão completa e o grupo que manteve lesões. Efeitos adversos foram relatados por 45% dos doentes, sendo ardor leve a moderado (25%), ardor intenso (7%), dermatite ulcerativa (8%) e efeitos sistêmicos (5%). **Conclusão**: O imiquimode foi efetivo no controle dos condilomas acuminados perianais recidivantes dos doentes HIV-positivo, independente da contagem sérica dos linfócitos T $CD4^+$.

Palavras-chave: infecções pelo papilomavírus; condiloma acuminado; imunoterapia.

INTRODUCTION

Human papillomavirus (HPV) is today one of the sexually transmissible agents of highest prevalence worldwide[1] and the most common in the perianal region[2-5]. More than 50% of all sexually active people are infected with HPV[6]; but most of them are asymptomatic, and only 10% present verrucous lesions, papilomata or dysplasias[3,7-9]. The anus is the extragenital site more frequently affected by HPV, and the most aggressive and recurrent disease occurs in patients that contract the disease through the human immunodeficiency virus (HIV)[3,8-14].

Among the several treatments for condylomata acuminata, the most frequent are ablative topical drugs (podophillin, trichloroacetic acid and podophyllotoxin), surgical procedures (with electrocautery, laser, infrared coagulation, cryotherapy and surgical excision) and immunotherapy (imiquimod and cidofovir).

Imiquimod, an imidazoquinoline (1-[2-methylpropyl)-1H-imidazole-[4,5-c]-quinoline-4-amine), is a chemotherapic and immunostimulant agent with antitumoral and antiviral activities[12,15]. It acts as an immunomodulator, due to the activity of toll-like receptor agonists on monocytes, macrophages and dendritic cells, activating the innate and cellular (Th1) immunity by inducing pro-inflammatory cytokines, such as interferon alpha, tumor necrosis factor-alpha and interleukins 1, 6, 8 and 12. In addition, it induces apoptosis and activates lymphocytes B, boosting the immunological response to cells altered by HPV[8,16-23].

Although the literature mentions that imiquimod promotes reduced incidence of recurrence, prolonged disease-free survival and qualitative and quantitative virus reduction[12,15,24-26], the studies presented some faults, as most of them are not prospective or randomized. In addition, they analyzed small samples, which were mixed in terms of the individual's immunocompetence, they omit the patient's prior treatments, they do not mention the lesion locations and involve short follow-up period. On the other hand, the cost is higher and the short-time effectiveness as the first-line treatment, is similar to that of cheaper topical drugs[27].

These doubts led to the proposal of this study, which evaluated the effectiveness of imiquimod in chronic and multi-recurrent perianal condylomata acuminata of HIV-positive patients.

CASE AND METHOD

That was a 12-month prospective clinical study, in which imiquimod 5% cream, topical use, was prescribed to 75 patients with recurrent perianal condylomata acuminata of difficult control, who had already been submitted to several other clinical and surgical treatments.

The study excluded from the initial sample ten patients that did not return for follow-up, three patients that did not use the product as prescribed and one patient who dropped out due to perianal discomfort. Then, the study included 61 patients who received care during the year of 2008, who used imiquimod for at least eight weeks and who accepted to be submitted to the study, signed an informed consent term and rigorously came to our outpatient clinic observing the follow-up period. The patients were 55 males and 6 females, mean age 40 years old, ranging from 22 to 63 years old.

The drug was applied (after medical instruction) at home, digitally, to the entire anal canal, by the patient or accompanying people. An envelope (250 mg) was used three times a week, on alternate days, for eight weeks.

The product effectiveness was evaluated 15 days after the end of the treatment, through a complete proctological exam, including anal colposcopy (high-resolution anuscopy) and anal canal scrape cytology,

in those patients that did not present macroscopic lesions. For this exam, we used the conventional colposcopy and applied 5% acetic acid and iodinated solution to identify the residual subclinical lesions. Those with persistent disease, either macroscopically or microscopically, received the drug for other eight weeks and were again submitted to clinical evaluation, colposcopy and scrape cytology 15 days after the end of the treatment.

In the product effectiveness evaluation, the study considered remission or complete response when no clinical or subclinical lesions were present, and remission or partial response when the clinical disease was reduced to half the initial involvement. Those with continued manifestations or reduced by 50% were considered as without remission or no response.

We evaluated again all patients with complete remission through proctologic exams and colposcope and acetic acid, six month after the end of the treatment. We considered as recurrence when the patient presented macroscopic or microscopic lesions after complete remission. We studied about the adverse effects of the product.

Finally, we compared the group with complete remission to the others, including partial remission and no response, regarding $CD4^+$ T lymphocyte count.

The Student's *t*-test was used in the statistical analysis of the study.

RESULTS

After 8-week treatment, we observed 33% (20 cases) of complete remission, 51% (31 cases) of partial remission and 16% (10 cases) of patients without remission. When including the patients that used the product for 16 weeks, we have: 46% (28 cases) of complete response, 44% (27 cases) of partial response and 10% (6 cases) without response.

The recurrence rate in those patients with complete response was 11% (3 cases), 2 of them used imiquimod for 8 weeks and presented recurrence within 16 and 24 weeks, and one used it for 16 weeks and presented new lesions within 24 weeks.

Regarding the serum level of $CD4^+$ T lymphocytes, no statistically significant difference was observed, using the Student's *t*-test (p=0.110), between the group with complete remission after 16-week treatment (mean level of $CD4^+$ T lymphocytes: 398 cells/mm^3) and the group that remained with lesions (324 cells/mm^3).

Adverse effects were reported by 45% of the patients. The most frequent were mild to moderate burning (25%), intense burning (7%), ulcerative dermatitis (8%) and systemic symptoms (5%). The systemic effects in our sample occurred in two patients. One reported symptoms of flu syndrome and one presented erythema nodosum on the right leg.

DISCUSSION

The literature shows conflicts regarding the best therapy for anal condylomata acuminata, with some authors indicating topical substances as the first-line method[8,28-31] and others, the surgical ablation[32-34]. Our study showed better results when we started with the topical treatment (podophyllin 25% below the pectineal line and trichloroacetic acid 95% above this line), with 50% of complete remission and two-fold disease-free survival when comparing it to ablative techniques[29]. The recurrence rate was reduced from 76% with the ablative treatment to 51% with the topical treatment[29], placing the surgery as a second-line treatment option in our service.

We indicated the topical treatment even in case of large lesions, as we observed that it promotes reduction of lesions, enabling easier surgical treatment subsequently, when required, eliminating the coexisting subclinical disease, and the postoperative pain[8,9,35] and extending the disease-free survival[9,29].

When comparing studies that use ablative techniques to those that use imiquimod, as the first-line treatment option, a longer disease-free survival was observed with the imiquimod; 45 to 79% recurrences with surgical procedures[36,37] and 65% with infrared[38,39], while only 26 to 29% was observed with the use of imiquimod[15,40].

Controlled studies showed the same effectiveness of podophyllin and imiquimod when evaluating healing rates, but the latter involved higher costs[41]. We opted for imiquimod to patients with multi-recurrent lesions[8,35] to promote better local immunity and enable recurrence control.

While some studies prescribed imiquimod to HIV-positive patients for the treatment of subclini-

cal lesions to reduce the viral load of HPV[15], others did not show statistical significance versus placebo, despite their small sample[42]. Our study, on the other hand, showed good effectiveness of the product, although it was only indicated to multi-recurrent condylomata acuminata in HIV-positive patients.

The permanent HPV infection is due to repeated sexual contact, virus location far from lymphatic tissues, deep or forgotten lesions, latent form of the virus, long incubation period of HPV and alteration to the local immunity[8,43]. There is no evidence that the condylomata acuminata treatment will eliminate the viral infection (latent form), but that it may eliminate its clinical form (macroscopic lesion) and subclinical form (microscopic lesion), reducing the patient's infectivity degree. Some studies with imiquimod showed qualitative reduction (decrease in more virulent strains) and quantitative reduction (decrease in the number of coexisting infectious types) different from the other forms of treatment[12,15,44,45].

In our sample, we observed 90% of remission, with complete remission in 46% after 16-week treatment with imiquimod. Recurrences occurred in 11% of the patients, up to 6 months of follow-up. These numbers agree with the literature, which shows remission between 74 and 84%, with complete remission between 25 and 77% of the patients[12,15,40,45,46].

It is interesting to point out that we obtained 33% of complete response after 8-week treatment, which occurred in 46% after 16-week treatment, determining gains over one third. All patients with complete remission after an additional 8-week treatment, except for one case, presented partial response in the initial treatment. It suggests that extending the treatment to 16 weeks benefits especially those patients with partial remission in the initial treatment.

Some studies with immunocompetent patients with HPV caused by anal and genital contact, showed 50 to 64% of complete response in the 16-week treatment with imiquimod and recurrence rate of 13%, as well as 28% of adverse effects, such as local erythema and superficial cutaneous ulcerations[43-45]. On the other hand, another study comparing immunocompetent to immunodepressed patients showed a remission rate of 62% in the first group and 31% in the second, with higher recurrence rate in the second[46].

A prospective study with HIV-positive patients using imiquimod as first-line treatment observed 77% complete remission, with 26% recurrence in the long term (mean follow-up of 20.6 months)[12,15]. In this study, as the patients were typified according to their viral DNA, the authors observed 58% of new lesions in non-treated sites, which shows a high number of patients with either new or recurrent lesions at the end of the follow-up period[12]. We criticize such differentiation (new and recurrent lesion), as, in fact, the strains coexist and, sometimes some viral types show clinical lesion and sometimes other types do. This differentiation collaborated to a rate of complete remission in this study much above the mean value of the studies in the literature, including our finding.

In our study, the patients with recurrent lesions showed statistical significance regarding the levels of $CD4^+$ T lymphocytes, unlike the patients who presented new lesions[12,15]. However, neither the lesion location (anal canal or margin), nor the dysplasia degree influenced the response[12].

Another study that analyzed a higher number of HIV-positive patients found the same rate of complete remission as ours (46%), in a 20-week treatment with imiquimod, with higher recurrence rate (29%), but with a longer follow-up period[40], suggesting that we should follow our patients for a longer period to obtain the true recurrence rate. In fact, we have followed up the patients whose lesions were eradicated, each six months, with anal colposcopy and oncotic cytology of the anal canal and, after three negative exams, once a year. However, most patients with recurrent lesions, have it within 12 months.

Although the literature shows evidence that serum levels of $CD4^+$ below 200/mm^3 are associated with higher recurrence rates[36,45], our study did not show statistical difference regarding the level of $CD4^+$ between the group with complete remission and the others. Another study conducted by our team with imiquimod observed no statistical significance between the response and the level of $CD4^+$, nor between the side effects[46]. Other authors also found similar results to ours, i.e., no association with $CD4^+$ or viral load[40]. This result is expected, as most of the studied sample (72%) presented $CD4^+$ counts above 200 cells/mm^3, like most studies that have been published. It occurs because today, the patients that seek services to treat

anal condilomatosis have the lesion caused by HIV infection, which is controlled with antiretroviral (ARV) drugs, and without systemic opportunistic diseases. The impact of ARVs on the prevention and control of opportunistic diseases is known; but the impact is different in HPV infection[47].

Regarding the adverse effects, they were reported by 45% of the patients, but most of them presented only mild to moderate burning (25%), which many times is not considered an adverse effect by the literature, as it is the expected response in these cases. Local erythema occurred in all patients submitted to the treatment[12], which is not necessarily a complaint of the patient. Ulcerative dermatitis corresponded to 8% of the adverse effects and the flu syndrome to 3%. The study also observed erythema nodosum on the leg of one of our patients. Such findings confirm with the literature, which reports 50% of adverse effects - 32% of ulcerative dermatitis and 18% of flu syndrome[2,15], values much higher than those found in our study.

CONCLUSION

Imiquimod was effective in the remission of recurrent perianal condylomata acuminata in HIV-positive patients.

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