Original article
UDC: 616.988.2:618.1



# A phase II trial of Ribavirin (Virazole®) in patients with genital infection caused by human papillomaviruses

**Violeta STANIMIROVIĆ**[1]
**Branko STANIMIROVIĆ**[2]
**Dejan NIKOLIĆ**[3]
**Aleksandra NIKOLIĆ**[4]
**Spomenka CUCAK**[1]

**BACKGROUND:** *Human papillomaviruses (HPV) are widely spread all over the world, particularly in young, sexually active persons. Diseases caused by them are highly contagious. Latent period can vary from several months to several years. A larger number of HPV (22 types) infect mucous membranes of the genital tract and due to their high oncogenic potential, the presence of these viruses in the genital tract represents a medium for developing premalignant and malignant lesions. Different treatments were used in the therapy of HPV infections: chemical, ablative and immunotherapy. This study was conducted in order to evaluate efficacy and predict the response rate to ribavirin (Virazole®) in patients with genital infection caused by HPV, types 6 and 11, as well as to determine the tolerance of this drug in the study group.*

**METHODS:** *During the single-center, open-label controlled study 50 eligible patients were treated with ribavirin (Virazole®) 7.5% cream, applied in a thin layer on each HPV lesion 3 times a day, during 28 days. Patients were considered eligible according to the presence of the clinical and subclinical forms of HPV (types 6 and 11) changes, detected on the skin and mucous membrane of the lower genital tract. These changes had been clinically and/or colposcopically confirmed before the treatment, as well as virologically verified (HPV DNA in situ hybridization technique).*

**RESULTS:** *Partial clinical and/or laboratory response to treatment was detected in 96% patients. The onset of the total lesion area regression occurred after day 14 of the treatment. After the end of treatment, virological analysis showed decreased positiveness of HPV types 6 and 11 results, however this was not statistically significant. Local symptoms relief began to appear after 8 days of treatment. After 14 days of treatment, 96% of patients responded to therapy, and after 21 days, all patients were without symptoms.*

**CONCLUSION:** *This study is a good basis for further research in treatment of HPV genital infection by ribavirin.*

**KEY WORDS:** *Ribavirin; Papillomavirus, Human; Genital Diseases, Female; Condylomata Acuminata*

*Archive of Oncology 2001,9(2):89-94©2001, Institute of Oncology Sremska Kamenica, Yugoslavia*

[1]GALENIKA R&D INSTITUTE, BELGRADE, YUGOSLAVIA
[2]UNIVERSITY GYN/OB CLINIC "NARODNI FRONT", BELGRADE, YUGOSLAVIA
[3]CLINICAL CENTER "BEŽANIJSKA KOSA", BELGRADE, YUGOSLAVIA
[4]CLINICAL CENTER "DEDINJE", BELGRADE, YUGOSLAVIA

## INTRODUCTION

Human Papillomaviruses (HPV) are widely spread all over the world, particularly in young, sexually active persons. Diseases caused by these viruses are highly contagious (1,13,14,15,19). Latent period can vary from several months to several years. Infections of the newborns are possible during their passage though birth channel (2). HPV are 12 times more frequent causes of genital infections than herpes simplex genitalis (3,16). The prevalence of papillomavirus infections in developed countries is around 10% in males and females between 15 and 50 years of age (4,17). HPV belongs to papova viridae family. These are viruses of 52-55 microns in size, having cubic symmetry with DNA genome and protein cover (5).

Hybridization techniques used so far (Dot blot, Southern blot, PCR and in situ hybridization) revealed 72 HPV types. Some of these (types 1, 2, 3 and 4) show skin affinity where, by infecting the layers of plate-shaped epithelium and by horning them, cause the formation of veruccae vulgaris. Types 6 and 11 infect the plate-shaped layers of epithelium as well as the mucous membranes of

Address correspondence to:
Dr Violeta Stanimirović, Batajnički drum b.b., 11080 Belgrade, Yugoslavia

The manuscript was received: 17. 04. 2000.
Provisionally accepted: 21. 03. 2001.
Accepted for publication: 28.05. 2001.

predilection sites causing proliferative changes (6,7,18).

A larger number of HPV (22 genotypes) infect mucous membranes of the genital tract. Because of their high oncogenic potential, the presence of these viruses in the genital tract represents a medium for developing premalignant and malignant lesions (dysplasia and carcinoma: cervical-CIN, vaginal-VAIN, vulvar-VIN and penile-PIN) (8,13,17,18).

The most frequent carcinogenic types (16 and 18) are likely to be found in 70% to 80% of cervical carcinoma, while the others are found in approximately 15% of such tumors (9,10,20). It is known that these viruses penetrate though the skin and/or mucous membranes to the depth of 50 to 150 microns.

Co-carcinogens of physical, chemical or hormone nature can influence the transformation of thus changed cells into a malignant phenotype (11). Different treatments were used in the therapy of HPV-caused infections: chemical, ablative and immunotherapy (12,21). $CO_2$ laser therapy proved to be the most successful so far and is accepted as a referent treatment method.

The objective of the study was to determine the efficacy and predict the response rate to ribavirin in patients with genital infection caused by HPV, types 6 and 11, as well as to determine the safety of the study drug in these patients. Response criteria for the evaluation of the study objectives were as follows:

*For efficacy:* The primary endpoint is disappearance (or decrease in number and size) of all clinically and colposcopically detected HPV changes on the lower genitals.

*For safety:* Local and systemic tolerance and changes in the laboratory parameters.

## MATERIALS AND METHODS

In this pilot study, the observed clinical diagnoses were: condylomata acuminata and vulvitis condylomatosis. HPV lesions (caused by types 6 and 11) were located at: labia minora, labia majora, regionis clitoridis and regions fossae navicularis.

Treated lesions were manifested as: single warts, multiple warts and conglomerates. Total treated genital region area was up to 2 $cm^2$. Total number of treated lesions was up to 5.

The study analysis included 50 eligible female patients, aged 18 to 65, with present prodromal signs of clinical and subclinical, individual or multiple forms of HPV changes on the skin and mucous membrane of the lower genital tract (vulva, introitus vaginae, perineal and perianal region) diagnosed as: condylomata acuminata and vulvitis condylomatosis.

The study drug was ribavirin (Virazole®), 7.5% cream, in 15 g tubes. Each gram of cream contained 75 mg of active principle in an emulsified medium. Ribavirin, 1-ß-ribofuranosyl-1,2,4-triazole-3-carboxamide, is a synthetic purine nucleoside, whose chemical structure resembles that of guanosine, xantosine and pirazomycin. It is white, odorless, tasteless crystalline powder, practically insoluble in organic solvents but readily soluble in water. Ribavirin is a broad-spectrum antiviral agent which, after intracellular phosphorylation to mono-, di- and especially triphosphate nucleoside structures, exerts its virustatic rather than virucidal activity on several intracellular levels by mechanisms which are still elusive.

Ribavirin 7.5% cream contains 75 mg/g of active principle in emulsified medium.

**Table 1.** Study flow chart

| Parameter | Baseline | Treatment period | | | | | Post-treatment period | |
|---|---|---|---|---|---|---|---|---|
| | Day 0 | Day 1 | Day 8 | Day 14 | Day 21 | Day 28 | Day 42 | Day 56 |
| Medical history and physical examination | x | | | | | | | |
| Pregnancy test | x | | | | | | | |
| Clinical diagnosis | x | x | x | x | x | x | x | x |
| Cytological diagnosis | x | | | | | | | x |
| Colposcopic diagnosis | x | x | x | x | x | x | x | x |
| HPV DNA hybridization *in situ* | x | | | x | | x | | x |
| Erythrocytes | x | | | | | x | | x |
| Hematocrit | x | | | | | x | | x |
| Hemoglobin | x | | | | | x | | x |
| Sedimentation rate | x | | | | | x | | x |
| Leukocytes and differential count | x | | | | | x | | x |
| Platelets | x | | | | | x | | x |
| Plasma haptoglobin lv. | x | | | | | x | | x |
| ALT | x | | | | | x | | x |
| AST | x | | | | | x | | x |
| Alkaline phosphatase | x | | | | | x | | x |
| Total bilirubin | x | | | | | x | | x |
| Na, Cl, K, bicarbonate | x | | | | | x | | x |
| BUN, creatinine, urate | x | | | | | x | | x |
| Total protein | x | | | | | x | | x |
| Urinalysis | x | | | | | x | | x |

After baseline screening and obtaining the values for all endpoints displayed in the study flow chart (Table 1), patients entered the treatment period (28 days), and the followed-up period (from day 29 to day 56). On days 1, 8, 14, 21, 28, 42 and 56 patients were visited by the study physician. During these visits clinical and colposcopical examinations were performed. The purpose of the clinical examination was to diagnose the presence of individual and/or multiple genital warts, their tendency to spread toward the perineal or perianal region, to detect the potential presence of ulcerations and of secondary infections, to detect potential mechanical obstruction in urethral or anal channel due to wart size as well as to detect vaginal and/or urethral flux and postcoital bleeding. The surface area of each lesion was assessed by multiplication of the longest and widest diameters of changes. The total lesion covered surface area was expressed as the sum of individual lesion surface areas.

The purpose of colposcopic examination was to asses the HPV genital changes (localization, size and type). Colposcopic examination was performed one minute after the application of 3%

acetic acid on a clinically identified HPV changes of a subclinical lesion. A clear whitish reflection was shown in the region of change as a result of being soaked with acetic acid ("acetowhitening"). Acetowhitening represents a focus of epithelial hyperplasia. Virologic verification of HPV DNA was performed by *in situ* hybridization technique. The swab specimens for virologic analysis were collected from the genital warts before the treatment (day 0), in the middle of the treatment period (day 14), at the end of the treatment (day 28) and after the follow-up period (day 56). During the study the following laboratory analyses were performed: hematologic (red blood cells - RBC, hematocrit, hemoglobin, sedimentation rate, white blood cells - WBC, differential count, platelet count); clinical chemistry (plasma haptoglobin levels, alanine aminotransferase - ALT, aspartate aminotransferase - AST, alkaline phosphatase, total bilirubin, sodium -Na, potassium - K, chlorine - Cl, bicarbonate, blood urea nitrogen - BUN, creatinine, uric acid, total protein by electrophoresis) and urinanalysis. The above laboratory analyses were performed before the initiation of treatment (day 0), at the end of the treatment (day 28) and at the end of the follow-up period (day 56).

Disease evaluation was performed according to clinical, cytological, colposcopic and virological diagnosis, as well as laboratory data (hematology, blood chemistry, urinalysis).

Evaluation criteria included: 1) degree of the lesion(s) regression (signs and symptoms) as determined clinically and colposcopically, 2) time (days) to the appearance of lesion regression, 3) time to the obtaining of negative virology findings (negativisation of the viral presence) at the sites of HPV lesions as detected at the beginning of the study and 4) time (days) to disappearance of potential atypia, cytologically confirmed.

Final evaluation of the study (day 56) was recorded as: 1) complete clinical and laboratory response, 2) complete clinical and incomplete laboratory response, 3) partial clinical and/or laboratory response, 4) stable disease or 5) progression. Local signs were clinically defined and evaluated as follows: ulceration, secondary infection, mechanical obstruction in the urethra or anal channel due to wart size, vaginal flux, urethral flux and post-coital bleeding. Local signs were rated as: absent, present but not interfering with daily activities and present, interfering with daily activities. Screened local symptoms were: pain in the affected region, aching on the affected region, itching in the region, dysuria, disturbed defecation. Local symptoms were rated as: absent, can be often ignored, persistent but not interfering with daily activities, persistent, interfering with daily activities.

### Adverse effects

The investigator had to make a medical judgment of the relationship of the adverse events to the study medication as: probable (reasonable evidence exists to assume a causal relationship), possible (the event is not easily explained by the patient's condition or other treatment and a causal relationship cannot be excluded), unlikely (most likely related to an existing etiology or other concomitantly administered drug other than the study medication; however, a causal relationship to the drug cannot be excluded) and unrelated (reasonable evidence exists that the event is attributable to other diseases or treatments).

## STATISTICAL DATA

Over 25,500 study data were statistically analyzed. Statistical methodology included description of all baseline parameters and comparison of the differences between the visits within the group for all efficacy and safety parameters. The following statistical methods were used: descriptive - Average (X) and Median (Med), Standard Deviation (SD), Standard Error (SE) and Range (Rang) and analytical - Friedman Two-Way ANOVA Test, ANOVA for repeated measures test, Cochran Q Test, Wilcoxon Signed-Ranks test, t-test for paired samples and McNemar test.

## RESULTS

Patients' lesion area began clinically to decrease after 14 days of treatment, the statistical significance was <0.01 (Table 2, Figure 1).

**Table 2.** Total lesion area

| Day | N | X ± SE | med (Rang) | Day/Day0 X (rang) |
|---|---|---|---|---|
| 0 | 50 | 0.7410 ± 0.1223 | 0.40 (0.05 - 4.15) | |
| 1 | 50 | 0.7430 ± 0.1222 | 0.43 (0.05 - 4.15) | 1.0050 (1.00-1.25) |
| 8 | 50 | 0.7454 ± 0.1221 | 0.43 (0.07 - 4.15) | 1.0180 (1.00-1.50) |
| 14 | 50 | 0.6014 ± 0.1147 | 0.36 (0.05 - 4.15) | 0.7867 (0.40-1.20) |
| 21 | 50 | 0.5076 ± 0.1033 | 0.26 (0.05 - 4.15) | 0.6641 (0.21-1.20) |
| 28 | 50 | 0.4402 ± 0.1019 | 0.23 (0.04 - 4.15) | 0.5463 (0.16-1.20) |
| 42 | 50 | 0.3556 ± 0.0581 | 0.21 (0.04 - 2.09) | 0.5094 (0.16-1.20) |
| 56 | 50 | 0.3560 ± 0.0581 | 0.21 (0.04 - 2.09) | 0.5154 (0.11-1.20) |

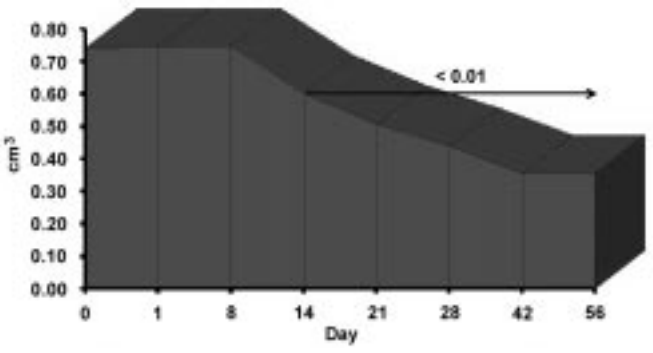


**Figure 1.** Total lesion area regression

Ten out of fifty patients had clinically detected lesion decrease of 50-60%. In two groups, eight patients out of fifty had lesion decrease of 40-50% and 30-40%, respectively. In three groups, with four patients in each, decrease of lesion was from 80-90%, 70-80% and 10-20%, respectively (Figure 2).

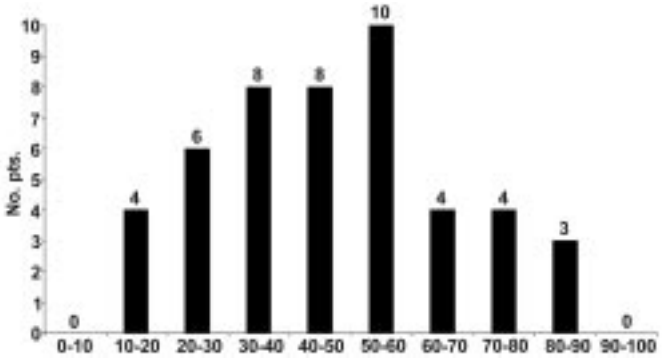


**Figure 2.** Distribution of lesion reduction

At the beginning of the study normal cytological diagnosis was reported in thirty-nine (78%) patients. At the end of study forty-six (92%) patients had normal cytological result (Table 3).

**Table 3.** Cytological diagnosis

| | Day 0 | Day 14 | Day 28 | Day 56 |
|---|---|---|---|---|
| Negative | 6 (12%) | 5 (10%) | 11 (22%) | 13 (26%) |
| 6 or 11 positive | 44 (88%) | 45 (90%) | 39 (78%) | 37 (74%) |
| Total | 50 (100%) | 50 (100%) | 50 (100%) | 50 (100%) |

Colposcopical finding was normal in forty-three patients (86%) at the beginning of the study. After 8 days of treatment the finding was normal in forty-eight patients ( 96%), and after 14 days of treatment all patients (100%) had normal colposcopic findings (Figure 3).

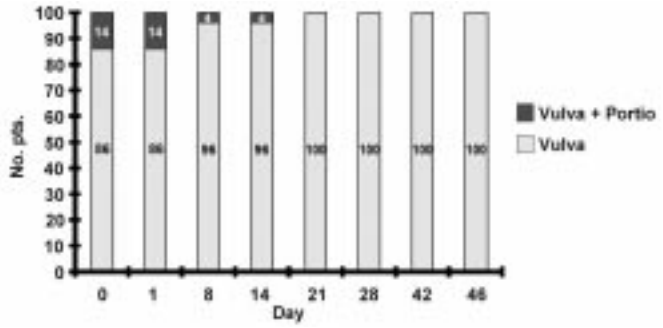


**Figure 3.** Localisation of colposcopic changes

Virologic testing from lesion swabs for HPV types 6 and 11 proved to be negative in five patients (10%) after 14 days of treatment; in additional eleven patients (22%) after 28 days of treatment, and in additional thirteen patients (26%) at the end of treatment (Table 4).

**Table 4.** Virological diagnosis - HPV types

| | Day 0 | Day 14 | Day 28 | Day 56 |
|---|---|---|---|---|
| Negative | 6 (12%) | 5 (10%) | 11 (22%) | 13 (26%) |
| 6 or 11 positive | 44 (88%) | 45 (90%) | 39 (78%) | 37 (74%) |
| Total | 50 (100%) | 50 (100%) | 50 (100%) | 50 (100%) |

Local symptoms (pain, aching, and itching in the affected region, dysuria, disturbed defecation), began to disappear after 8 days of treatment, in four patients (8%) the symptoms were present but did not interfere with daily activities, while twenty-six patients (52%) had symptoms that could be ignored. Pain in the region with HPV lesion was reported in one patient (2%), aching in twenty-six patients (52%) and itching in twenty-four patients (48%). After 14 days of treatment forty-seven out of fifty patients (94%) had no symptoms, with only three patients (6%) having some symptoms (pain, aching), that could be ignored according to the evaluation criteria ("present, but can be often ignored"). After 21 days of treatment no patients had any symptoms caused by HPV (Table 5). Dysuria and disturbed defecation were not reported.

**Table 5.** Local symptoms

| | Day 0 | Day 1 | Day 8 | Day 14 | Day 21 | Day 28 | Day 42 | Day 56 |
|---|---|---|---|---|---|---|---|---|
| Absent | 11 (22%) | 11 (22%) | 20 (40%) | 47 (94%) | 50 (100%) | 50 (100%) | 50 (100%) | 50 (100%) |
| Present, but can be often ignored | 11 (22%) | 11 (22%) | 26 (52%) | 3 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Present, but does not interfere with daily activities | 28 (56%) | 28 (56%) | 4 (8%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Present, interfere with daily activities | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Treatment outcome: forty eight-patients (96%) had partial clinical and/or laboratory response related to virological results), while only two patients (4%) had stable disease at the end of the study (Table 6).

**Table 6.** Treatment outcome

| | N | % |
|---|---|---|
| Complete clinical and laboratory response | 0 | 0.0% |
| Complete clinical and incomplete laboratory response | 0 | 0.0% |
| Partial clinical and/or laboratory response | 48 | 96.0% |
| Stable disease | 2 | 4.0% |
| Progression | 0 | 0.0% |

According to patient's subjective evaluation, twenty-five of them (50%) had an impression of a considerable improvement; according to the investigator's evaluation a considerable improvement was also observed in 50% of cases after the treatment (Tables 7 and 8).

**Table 7.** Patient´s subjective evaluation and investigator´s evaluation

| | N | N | % |
|---|---|---|---|
| Cured | 0 | 0 | 0.0% |
| Considerable improvement | 25 | 25 | 50.0% |
| Improvement | 23 | 23 | 46.0% |
| Unchanged | 2 | 2 | 4.0% |
| Worsened | 0 | 0 | 0.0% |

**Table 8.** Time to partial regression appearance

| Day | N | % |
|---|---|---|
| 2 | 1 | 2.1 |
| 14 | 32 | 66.7 |
| 21 | 11 | 22.9 |
| 28 | 4 | 8.3 |
| X ± SD | 16.52 ±4.97 | |
| Med. (rang) | 14 (2-28) | |

After 14 days partial regression was reported in thirty-two patients; additional eleven patients took 21 days of treatment for partial regression, while three patients required 28 days of treatment for partial regression to occur (Table 9).

**Table 9.** Post-treatment intervention

| | N | % |
|---|---|---|
| $CO_2$ laser vaporization | 32 | 64.0% |
| Termocauterization | 18 | 36.0% |

According to the protocol, $CO_2$ laser or thermocauterisation treatment had to be done at the end of study in patients with incom-

plete lesion regression. In this study, thirty two patients (64%) completed their treatment with $CO_2$ laser vaporization, and eighteen patients (36%) with thermocauterisation treatment (Table 10).

**Table 10.** Post-treatment outcome

| | N | % |
|---|---|---|
| No visible warts | 33 | 66.0% |
| Reccurence of warts | 17 | 34.0% |
| Aggravation | 0 | 0.0% |

Abnormal laboratory values (RBC, WBC, Plt., Hb, ALT, AST) were not detected.

## DISCUSSION

In the mid-seventies of the twentieth century the epidemiological studies have been warning that cervical carcinoma is related to an unknown, sexually transmitted agent (1,3). Later, with the development of diagnostic procedures (especially in the field of virology), human papillomaviruses have been found to be responsible both for the skin and genital warts, and for malignancies on the genital tract (2,21). Only the development of recombinant DNA technologies made the identification of various types of HPV possible (5,6,8). Over 70 types of HPV have been identified to date, 35 of these being known to infect the genital tract. The method of HPV DNA in situ hybridization enabled the identification of HPV types of low malignant potential, namely: types 6,11,42,43 and 44. HPV types of higher malignant potential include:16,18,31,33,35,39,45,51,56,58,59 and 68 (10,15,20). The process of tumorogenesis of HPV-infected cell is a multistaged process, implying the induction of an abnormal DNA synthesis and cell proliferation (due to the presence of HPV genom). Non-viral factors contributing to this process are protoncogenes and alterations of tumor-supressor genes of the host cell (11). Genital warts are transmitted primarily by sexual contact. Following a single sexual contact with an infected person, HPV infection will occur in 60% of cases. Form of infection includes: clinical (manifested as genital warts), subclinical (lesions could be detected only after colposcopical examination) and latent (clinically tissue appears to be normal, however, virus is present and could be detected only by employing molecular biology methods). Following the primary infection, in the next three to nine months, clinically visible genital warts will develop in approximately 75% of infected sexual partners (4,20).

Various modalities are used in the treatment of genital warts, including topical (e.g. 5-fluorouracil, podophylotoxine, trichloracetic acid), intralesional (alpha-interferon), ablative (electrosurgery, criotherapy, $CO_2$ laser treatment), surgical (cold-knife excision) and systemic (vaccines) (5,6,21), however, none of these is ideal.

In this pilot study, clinical diagnoses that were observed were: condylomata acuminata and vulvitis condylomatosis. HPV lesions (caused by types 6 and 11) were located at: labia minora, labia majora, regionis clitoridis and regionis fossae navicularis.

Treated lesions were manifested as: single warts, multiple warts and conglomerates. Total treated genital region area was up to 2 $cm^2$. Total number of treated lesions was up to 5.

Many HPV treatments involve multiple and often painful treatments and all of them have restricted usability and flaws, in view of rate of successfulness (clinical eradication of warts) and the percentage of recurrences after certain time. Number of treatment modalities and their restrictions complicate the therapy which has to be individually adjusted to the severity of the disease, anatomical localization of the lesion as well as to the clinical course. Possible adverse effects, patient's tolerance, compliance, cost-effectiveness and cost-benefit ratio of the therapy must also be considered. Standard therapies offer the relief of symptoms, but they cannot ensure permanent remission.

## CONCLUSION

Ribavirin is a broad-spectrum antivirotic, structurally similar to cellular ribonucleosides, with a proven virostatic, cytostatic and immunological activity (22,23). This pilot study, which was the phase IIa of a clinical pharmacological scale of the drug development, showed that ribavirin could be effective in the treatment of HPV genital lesions caused by low-oncogenic types 6 and 11, as partial clinical regression of genital warts was recorded. $CO_2$ laser therapy still remains the relevant treatment for clinical eradication of genital warts for lesion larger than 0.5 $cm^2$. This was the reason why this ablative technique was used for elimination warts remaining after ribavirin treatment. Minor warts (smaller than 0.5 $cm^2$ ) were treated with thermocauterization.

The effect of ribavirin (Virazole®) on HPV genital lesions (type 6 and 11) was evident. Clinically detected HPV genital warts regression was statistically significant. The onset of the lesion regression occurred after 8-14 days of treatment. Duration of regressive process on total lesion area lasted from day 8 to day 42 of the study. This study (clinical phase IIb) is a good foundation for further research in treatment of HPV genital infection by ribavirin. It gives the opportunity to consider new ribavirin studies that would investigate: larger sample size, the study drug with higher concentration of ribavirin (e.g. 20%), more available pharmaceutical formulation (e.g. gel), new administration routes of the study drug (probably intravaginal, or sublesional) and possible combination of interferons and ribavirin, in the treatment of severe forms of HPV genital lesions.

## REFERENCES


1. Bacton S. Viral infections of the genital tract (Review article).Current opinion in Infectious Diseases 1996;9:48-51.
2. Mosicki AB. Genital Human Papilloma Virus Infections. Adolescent Medicine, State of the Art Reviews. Hanley Belfus Inc.1990;1(3).
3. Bourne C, Mills J, Mindel A. Genital herpes and genital human papilloma virus infection (Review article). Current Opinion of Infectious Disease 1995;8:10-5.
4. Syrjanen KJ. STD and Anogenital Neoplasia: Epidemiology and Nodular History. In: 9th World Congress of Cervical Pathology and Colposcopy, Sydney, Australia, May,12-16,1996, Book of Abstracts. 1996. p.43
5. Stanimirović B. Virus infections of genital tract. Belgrade: Naučna knjiga; 1993. p.11-5.
6. Stanimirović B. Virus infections of genital tract. Belgrade: Naučna knjiga. 1993. p. 20-5.
7. Tabbara S, Salch A, Andersen A. The Bethesda Classification for Squamous Intraepithelial Lesions: Histologic, Cytologic and Viral C. Obs Gynec 1992;79:338-46.
8. Stanimirovic B, Grob R, Ruedlinger R. Human papillomaviruses and cervical neoplasms. Jug Ginekol Perinatol 1989;29:79-83.
9. Zur Hansed N. Condylomata Acuminata and Human Genital Cancer. Cancer Res 1976;36:530.
10. Duggan M. Human Papilloma Viruses in Gynecological Cancer (Review article). Current Opinnions Obst Gynecol 1991;8:56-62.
11. Yamashita T, Inoue Y, Fujinaga YS, Fujinaga K. Detection and Typing HPV Genome: Consensus PCR Method. Tanpakushitsy Kakusan Koso 1996;41:664-8.
12. Roy M. HPV Options for Management, 9th World Congress of Cervical Pathology and Colposcopy, Sydney, Australia, May 12-16, 1996, Book of Abstracts. 1996. p.56.
13. Schiffman M, Herrero R, Hildesheim A. HPV DNA Testing in Cervical Cancer Screening. JAMA 2000;283:87-93.
14. Nobbenhuis MA, Walboomers JM, Helmerhorst TJ. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. Lancet 1999;354:20-5.
15. Blattner WA. Human retroviruses: their role in cancer. Proc Assoc Am Physicians 1999;111:563-72.
16. Gross G. Do we need antivirals for genital herpes simplex virus and human papillomavirus infection? Int J Antimicrob Agents 1999;12(1):1-3.
17. Wright T, Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA Testing of Self-collected Vaginal Samples Compared with Cytologic Screening to Detect Cervical Cancer. JAMA 2000;283:81-6.
18. Cuzick J. Human Papillomavirus Testing for Primary Cervical Cancer Screening. JAMA 2000;283:108-9.
19. Walboomers JM, Jacobs MV, Manos MM. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12-9.
20. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49:33-64.
21. Sedlacek TV. Advances in the diagnosis and treatment of human papillomavirus infections. Clin Obstet Gynecol 1999;42:206-20.
22. Smith RA, Kirkpatric W. Ribavirin, a broad spectrum antiviral agent. London: Academic Press Inc; 1980. p. 1-80.
23. Reynolds, ed. Ribavirin. In: Martindale The Extra Pharmacopoea. 31st ed. London: Pharmaceutical Press; 1997. p. 437.