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SUMMARY

Human Papilloma Virus (HPV) is responsible for altering cell cycle regulation which can lead to the malignant transformation of the uterine cervix epithelium. Although less important than the association with cervical carcinoma, a link has also been established between HPV infection and the development of carcinomas in ano-genital areas other than the uterine cervix (anus, penis, vulva and vagina). The HPV genome is found in almost all cervical carcinomas. The vast majority of HPVs, however, are not oncogenic but instead induce benign lesions. The study was carried out in order to assess the effectiveness of a treatment aimed at the immunoprophylaxis of recurrences, as various studies have shown that a persistent HPV infection increases the risk of high-level Cervical Intraepithelial Neoplasia. There is also data that shows a correlation between the resolution of HPV infection and regression of lesions in the ano-genital area. Both male and female patients were studied and they were divided into four groups, to which a group of untreated patients was added (control group). **First Group:** males with florid lesions treated first with electrosurgical excision and then with TF 11 (Guna) therapy. **Second Group:** females with florid lesions treated first with electrosurgical excision and then with TF 11 therapy. **Third Group:** males with aceto-reactive plate lesions subsequently treated with TF 11 therapy. **Fourth Group:** females with positive PAP tests or biopsies for koilocytosis, without clinical signs, subsequently treated with TF 11 therapy. The patients in the control group were divided into four groups on the basis of their lesion type, without being included in the therapeutic protocol; they were observed in order to assess the development of the disease. All the patients attended an initial consultation and were then monitored after 1, 3, 6 and 12 months. The protocol provided for the administration of one tablet on Monday, Tuesday, Wednesday, Thursday and Friday for eight weeks, followed by one tablet on Monday, Wednesday and Friday for another four weeks. The treatment was repeated every three months by administering one tablet on Monday, Wednesday and Friday for four weeks. We obtained very satisfactory results from this study, as we saw the almost total disappearance of the viral HPV lesions in the patients to whom the therapeutic protocol had been applied. The electrosurgical treatment of florid lesions proved to be effective in eradicating visible florid lesions and any possible recurrences. By combining this with TF 11, we saw no signs of the persistence of the disease in 97% of the cases.

KEY WORDS

HPV, TRANSFACTOR, TF 11, CONDYLOMAS, IMMUNOPROPHYLAXIS, CERVICAL CARCINOMA

TRANSFACTOR 11 IN HPV VIRAL PATHOLOGIES

(SURVEY OF 160 CASES)

INTRODUCTION

Human Papilloma Virus (HPV) is involved in the genesis of a vast range of mucous, muco-cutaneous and cutaneous hypertrophic benign lesions, clinically defined as condylomas, verrucas and papillomas.

The involvement of HPV in the onset of neoplastic lesions in the same epitheliums is an important factor.

It is already a well-known fact that specific types of HPV have been identified as causal agents of more than **90% of uterine cervical carcinomas and 50% of all ano-genital tumours**; it is also estimated that they are involved in around 20% of all cutaneous tumours.

Human Papilloma Virus has a specific affinity towards the squamous epithelium or its progenitor cells (basal reserve cells). It is therefore responsible for altering cell cycle regulation, which can cause the **malignant transformation of the uterine cervix epithelium**.

The HPV genome can be found in almost all cervical carcinomas. The majority of HPV strains, however, are not

oncogenic but cause instead benign lesions.

Recent studies confirmed the existence of a close link between HPV and Cervical Intraepithelial Neoplasia. This link is even more significant than that established between tobacco and pulmonary carcinoma or between Hepatitis B and hepatic carcinoma.

A less important link – compared with the link concerning the cervical carcinoma – has also been established between HPV infection and the development of carcinomas in ano-genital areas other than the uterine cervix (anus, penis, vulva and vagina), as well as in non-genital areas (oral cavity and oesophagus).

The time period between exposure to the virus and appearance of a lesion, varies between a few weeks to several months (and more). Some studies (follow-up studies) on female subjects who have tested positive for the presence of HPV DNA, indicate a period included between 6 and 24 months **before** the cytological changes manifest themselves.

Some Authors maintain that the virus can remain in the epithelium for a prolonged period **without** causing any morphological anomalies, hypothesising that they are located in the basal reserve cells.

Other studies showed how a persistent HPV infection increases the risk of high-level Cervical Intraepithelial Neoplasia.

There is also data illustrating the correlation between the resolution of an HPV infection and the regression of cervical lesions.

CHARACTERISTICS OF THE VIRUS

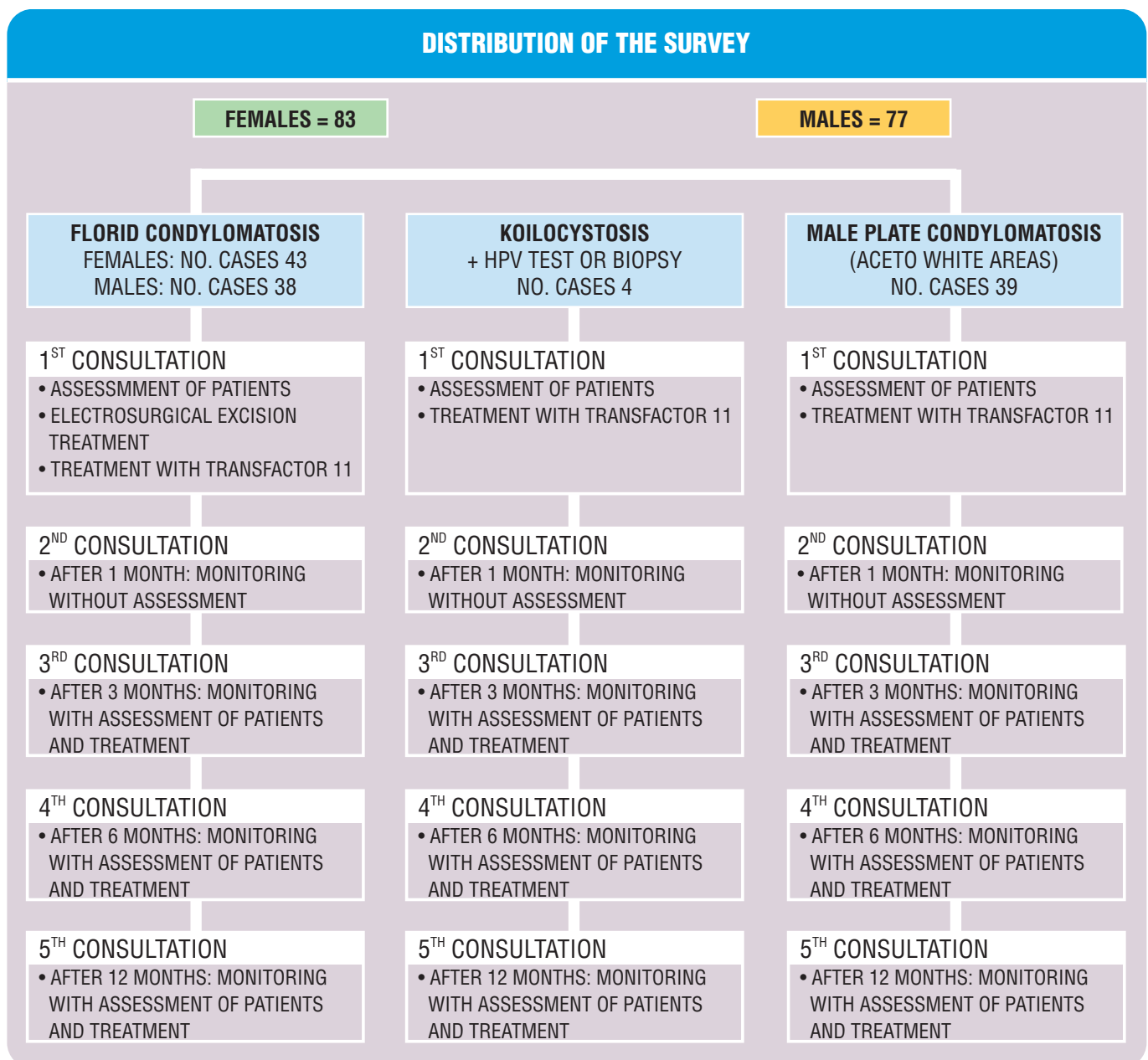
HPV is a **double helix DNA virus** of relatively small dimensions (55 nm. capsid; 8 kilobase genome). The DNA comprises three main regions: an “*upstream*” region, with regulation function, containing sequences that control transcription; an “*early*” region containing many of the genes involved in viral replication and, finally, a “*structural*” region. The latter comprises two parts: **L1**, the largest region, responsible for the formation of the capsid; and **L2**, responsible for the packaging of viral DNA with other gene products.

More than 100 types of Papilloma Virus have been identified, 40 of which can cause genital tract infections.

The acquisition of a viral, oncogenic-type increases the possibility of persistent infection which leads to viral integration and is a **predictive factor** of neoplastic progression that is more important in terms of viral load.

Approximately half the cervical carcinoma cases recorded worldwide tested positive for oncogenic HPV 16. Other important viral types associated with high risk are HPV 18, 31 and 45. HPV

Table 1



25, 31, 35, 39, 51, 52, 56, 58, 59, 68, 73 and W13b (very common) are high-risk viral types. A significant geographical variation in the prevalence of some oncogenic viral types has been established.

The integration of viral DNA into the host's genome begins in a late phase after HPV infection. Integration ensures the continuation of the expression of HPV E6 and E7 oncoproteins, which form complexes with tumoral inhibition proteins, expressed by the host, p53 and Rb, thus inactivating and altering the control of the cell cycle. The ensuing genetic instability can allow for increased cell and chromosome damage by the HPV and additional co-factors (e.g. smoking cigarettes), or causal mutations.

Fortunately, viral persistence to the point of integration is the exception rather than the rule. The majority of Papilloma Virus lesions leave a "window" open through which one can intervene.

Between the exposure to the virus and the development of the cancerous lesion, an evolutionary process takes place in successive stages that takes at least a **decade** to complete. This explains why uterine cervical carcinoma is a disease that occurs in middle age and elderly women rather than in 20-year-old women amongst whom there is the highest incidence of HPV infection. These aspects are fully taken into account by the doctors when treating adolescent or young patients.

MATERIALS AND METHODS

The study was carried out on a group of male and female patients aged between 16 and 47, in the period between 01.09.1998 and 30.04.2000.

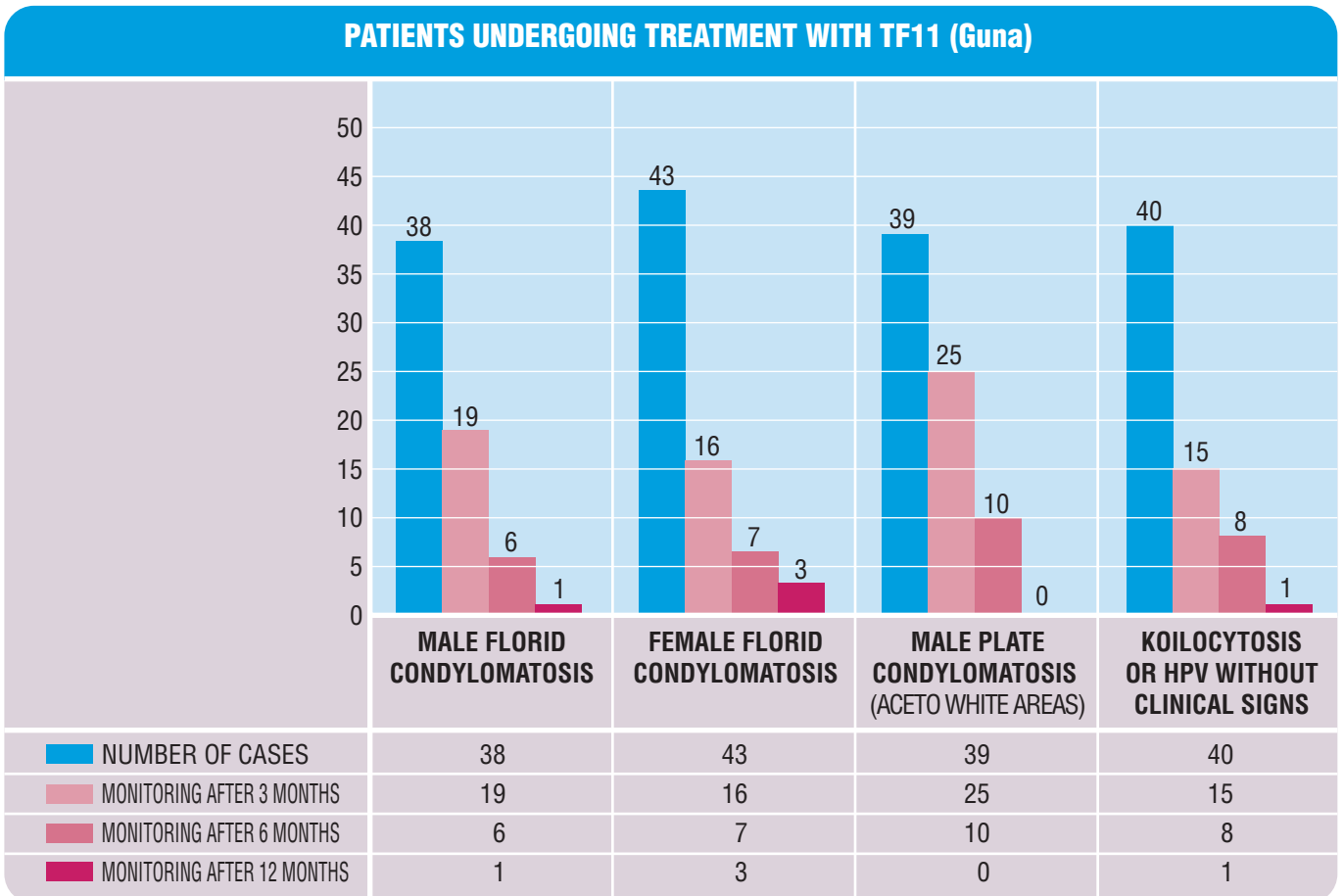
The examinations carried out (gynaecological examination, vulvoscopy, colposcopy, examination of male genitals, peniscopy, cytological and bioptic

tests) **recorded HPV-induced lesions.**

Both males (77) and females (83) were examined, and divided into four groups to which a group of un-treated patients (45) were added (TABLE 1):

- **First group** (38): males with florid lesions who were firstly treated with electrosurgical excision and then therapy with TF 11 (Guna) was introduced.
- **Second group** (43): females with florid lesions who were firstly treated with electrosurgical excision and then therapy with TF 11 was introduced.
- **Third group** (39): males with focal-type aceto-reactive flat lesions or lesions of the epithelium ranging from minimal size to rough (diameter between 2 to 30 mm), who began therapy with TF 11.
- **Fourth group** (40): females with positive PAP tests or biopsies for koilocytosis, without clinical signs, who began therapy with TF 11.

Table 2



The control group patients were divided amongst the four groups outlined above on the basis of their lesion type: they had not taken part in any therapeutic protocol and were examined in order to assess the development of the disease.

All the patients attended a first consultation. Checks were then made after one month (without assessing the effectiveness of therapy with TF 11), and after 3, 6 and 12 months when an evaluation of therapy with TF 11 was made. The protocol provided for the administration of one tablet on Monday, Tuesday, Wednesday, Thursday and Friday for eight weeks, followed by one tablet on Monday, Wednesday and Friday for another four weeks. The treatment was repeated every three months by administering one tablet on Monday, Wednesday and Friday for four weeks.

RESULTS

- ▶ The checks made **three months** after the beginning of treatment, showed a **persistence of recurrences** or **the presence of clinical HPV infection** in 75 out of 160 patients (47% of the survey) – in the first group (florid condylomas), there were 19 patients out of 38 (50%); in the second group (florid condylomas), there were 16 patients out of 43 (37%); in the third group (persistence of aceto white lesions), there were 25 patients out of 39 (64%); and in the fourth group (koilocytosis), there were 15 patients out of 40 (38%).
- When the patients were assessed after **six months**, the persistence of recurrences had been reduced to 19%, or 31 patients out of 160 – in the first group

there were 6 out of 38 (16%); in the second group, 7 out of 43 (16%); in the third group, 10 out of 39 (26%); and in the fourth group, 8 out of 40 (20%).

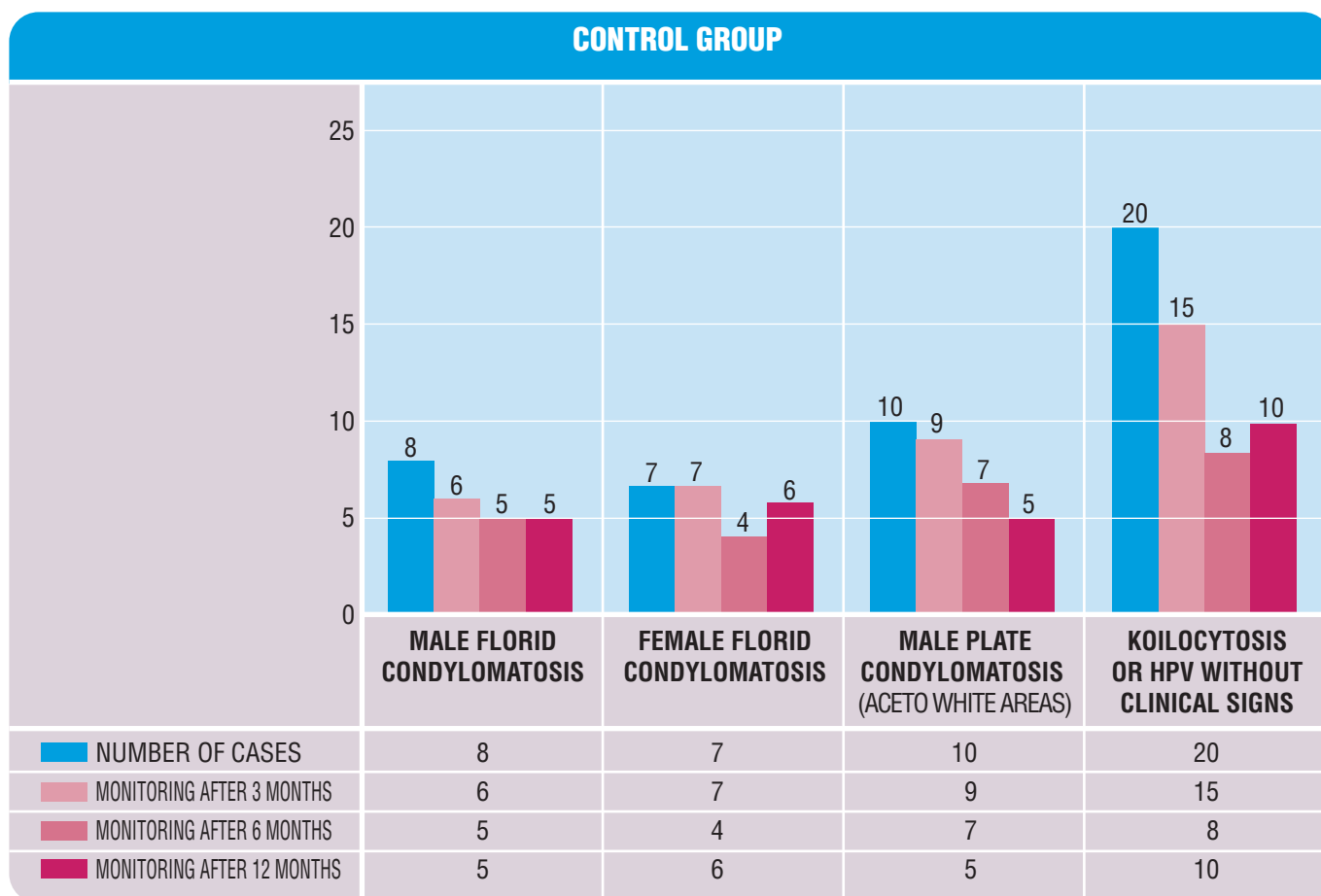
- After **12 months**, the persistence of recurrences was 3%, 5 out of 160 patients – in the first group, 1 out of 38 (3%); in the second group, 3 out of 43 (7%); in the third group, there were no recurrences; and in the fourth group, 1 out of 40 (3%) (see **TABLE 2**).

In the control group (45 patients), persistence of recurrences or the clinical presence of HPV at three, six and twelve months affected 37 patients (82%), 24 patients (53%) and 26 patients (58%) respectively (**TABLE 3**).

DISCUSSION

The aim of this study was to assess the effectiveness of a treatment aimed at the

Table 3



immunoprophylaxis of recurring HPV: various studies have shown that a persistent HPV infection increases the risk of high-level Cervical Intraepithelial Neoplasia. There is also data showing a correlation between the resolution of HPV infection and the regression of lesions in ano-genital areas.

The effectiveness of conventional non-immune treatments is **restricted by their topical therapeutic nature** – they can eliminate the lesions from HPV infection but it is well-known that they don't prevent recurrences even in the short-term. The use of **Interferon α** that can often eradicate a Condyloma via repeated intralesional infiltration or treatment using Imiquimod (5% cream), are not capable of preventing recurrences.

This disease, although not truly systemic, is regarded as a wider area of infection than those where there are visible lesions and a systemic treatment should, therefore, be prepared.

Various groups of researchers are currently focusing their attentions on preparing vaccines against HPV infection, with therapeutic or preventive action; however, they are still a long way from proposing truly effective molecules and their trials are still in Phase 1-2.

It will take many years before effective vaccines can be introduced; in the meantime, the only possible treatments are those using specific immunomodulators. **Transfactor 11 could be the ideal drug for a preventive approach to recurrences** and it also has no collateral effects. As a result, strengthening the immune defences using this therapeutic defence could be an effective weapon in preventing the recurrence of HPV infection.

CONCLUSIONS

This study has produced some very pleasing results, as it showed the **almost complete eradication** of HPV viral lesions in cases where the therapeutic

protocol was applied. The electrosurgical treatment of florid lesions has proved to be effective in eradicating visible florid lesions and recurrences (where applicable), in conjunction with TF 11.

In **97% of cases**, there were no longer any indicative signs of the persistence of the disease.

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