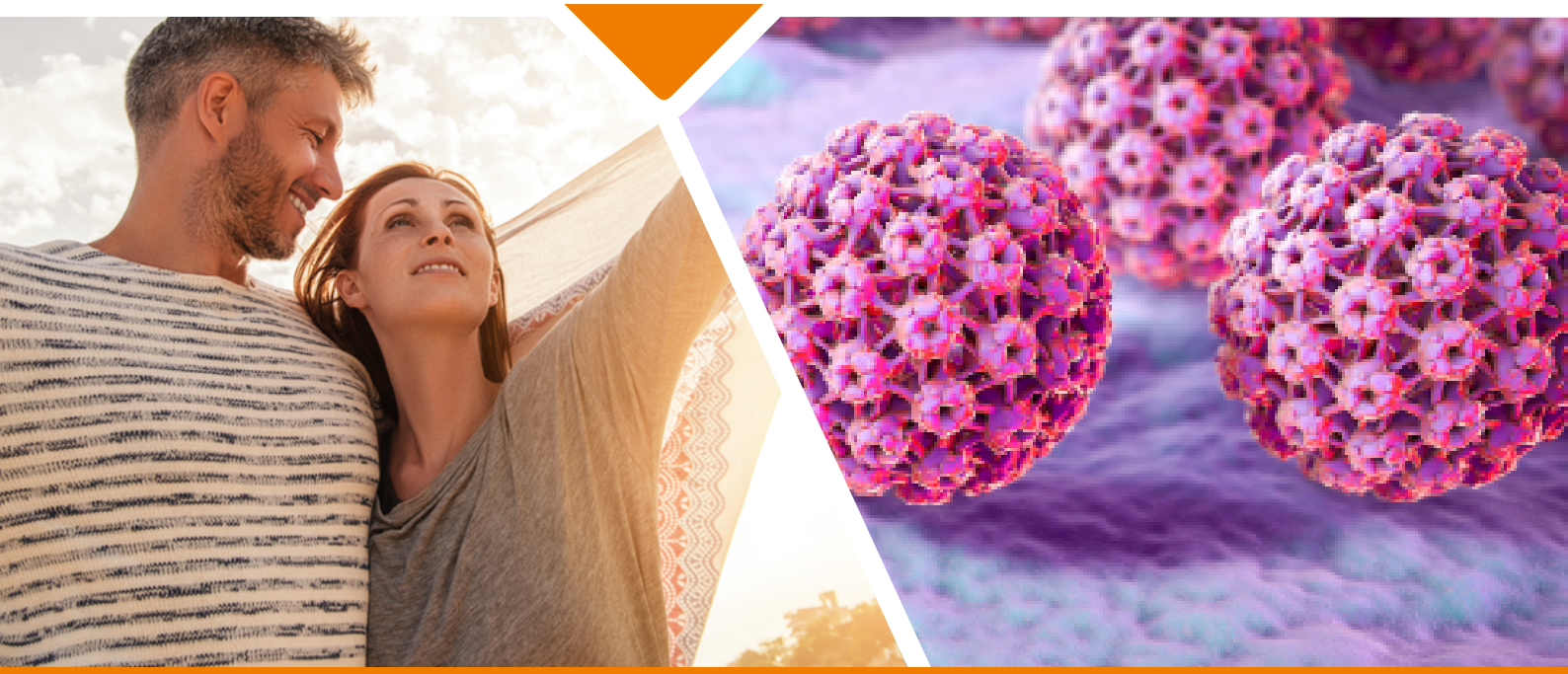
Micro-immunotherapy
International Medical Experience

Micro-immunotherapy & Anogenital Human Papillomavirus



Keep the virus in check

This brochure is for doctors and other health professionals only

List of abbreviations

APC	Antigen presenting cell
ASC-H	Atypical squamous cells, cannot exclude HSIL
ASCUS	Atypical squamous cells of undetermined significance
CIN	Cervical intraepithelial neoplasia
CMV	Cytomegalovirus
CsA	Cyclosporin A
EBV	Epstein-Barr virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HR-HPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesions
IFN-α	Interferon alpha
IL	Interleukin
LD	Low doses
LSIL	Low-grade squamous intraepithelial lesions
NK cell	Natural killer cell
PCR	Polymerase chain reaction

Immune support through **micro-immunotherapy** in anogenital HPV infections and associated diseases

Watch and Wait?

No!

Actively treat HPV infections with micro-immunotherapy, prevent complications and surgical interventions

APPLICATION* OF THE FORMULAS PAPI & C1

*According to the clinical experience of doctors of the International Associations of Micro-immunotherapy

FORMULA **PAPI**

Anogenital warts	1 capsule / day, for 3-6 months
Cervical dysplasia	1 capsule / day for at least 6 months

FORMULA **PAPI +** FORMULA **C1**

Cervical dysplasia as from PAPI IV or CIN II / CIN III or HSIL	1 capsule / day for at least 6 months
Anogenital and oropharyngeal carcinomas with confirmed HPV involvement	1 capsule / day for at least 6 months

Attention: Partner should be treated as well (1 capsule/day)

IMMUNOREGULATORY OBJECTIVES

- Block HPV proliferation and prevent infection of further cells
- Regulate immune function and dampen chronic inflammation promoting oncogenesis
- Prevent associated diseases

Testimonial

Micro-immunotherapy in HPV infections

"I began to study micro-immunotherapy intensively after I had treated a friend with the formula PAPI with surprising success. This friend's uterus was to be removed due to lesions associated with the human papillomavirus (HPV). As she had high-risk (HR) variants of HPV, there was a risk of them developing into cancer.

I had just heard about the immunoregulatory possibilities of micro-immunotherapy and recommended that she support her immune system against HPV through this therapy before considering surgery as a last resort. After only three months of treatment, the follow-up examination showed a reduction in the lesions. It was therefore no longer necessary to perform surgery.

I was very surprised by this case. As a doctor I was not aware that micro-immunotherapy could yield such positive results. Since then, I started to use this therapy more and more frequently and in many other areas, and it is now a cornerstone of my treatment strategy for various conditions."

Dr Josepa Rigau (Spain)

Introduction

This example from clinical practice illustrates the consequences of a HR-HPV infection and how micro-immunotherapy can help support the immune system to bring the infection under control. Experience has shown that complications and surgical interventions can thereby be avoided in most cases.

This brochure provides a detailed explanation of the micro-immunotherapy approach to HPV infections. For a better understanding of the mechanism of action, the most important characteristics of HPV and the role of the immune system are discussed first.

HPV Infections: A Brief Overview

HPVs are non-enveloped, double-stranded DNA viruses that belong to the Papillomaviridae family. To date, over 200 different HPV genotypes have been identified (40 of which are found exclusively in the ano-genital region)[1,2]. They infect multilayered squamous epithelia of the skin and mucosa, with DNA replication and protein expression being closely linked to the degree of differentiation of the infected keratinocytes (Fig. 1).

An HPV infection is not uncommon. In fact, it is one of the most common sexually transmitted infections worldwide. Almost every sexually active person is infected with genital HPV types at least once in their lifetime. Both men and women can become infected[1,2].

The risk factors for an HPV infection include a high number of sexual partners over the entire lifespan, oral and anal sex and a weakened immune system[2].

Most HPV infections are asymptomatic, with spontaneous healing occurring in around 90% of cases within a few months to two years if the initial immunological situation is good. However, depending on the HPV type, various clinical pictures can be triggered[1,2].

Low-risk HPV types (especially 6 and 11) trigger genital warts (condylomata acuminata). Although warts are relatively harmless, they are usually unpleasant for the person affected and can have a negative impact on their sex life and quality of life[1,2].

A chronic persistent infection with a high-risk HPV type (especially 16 and 18) can cause precancerous lesions in the multilayered epithelium, which can develop into cancer

over the course of several years. HR-HPVs are considered to be the main cause of cervical cancer, one of the most common forms of cancer in women. These virus types are also associated with the development and progression of other oncological diseases such as oropharyngeal carcinoma or penile, vaginal and vulvar carcinoma[1-4].

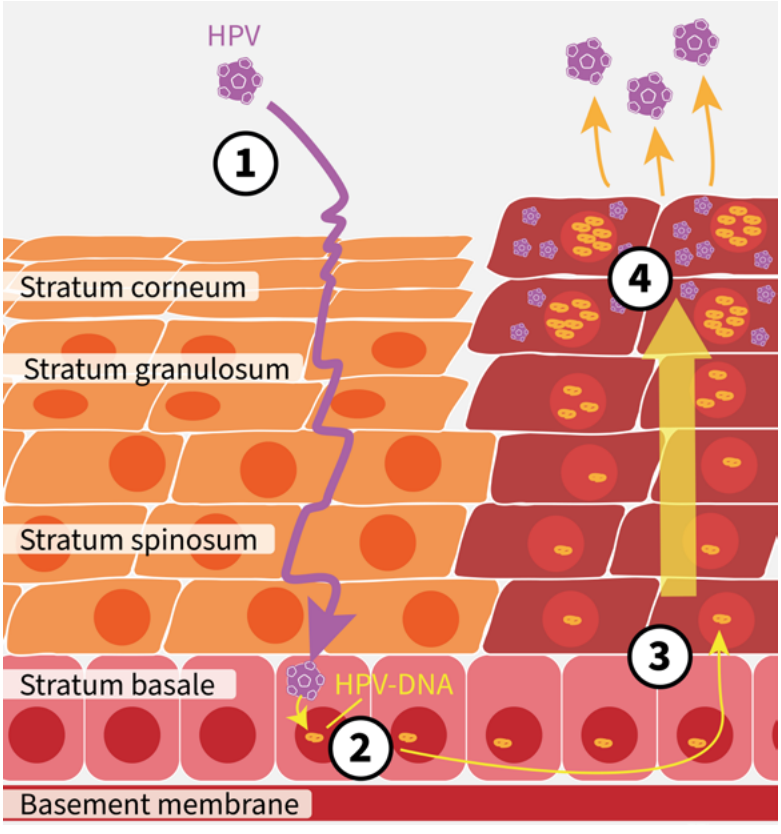
Role of the Immune System in HPV Infections

Both innate (e.g. dendritic cells, NK cells) and adaptive immunity (e.g. cytotoxic T cells) are of fundamental importance in HPV clearance[5]. As previously mentioned, this infection heals spontaneously and without consequences in most affected individuals.

However, with increasing age and due to other factors (including stress, environmental toxins, malnutrition), the immune system can run out of balance so that papillomaviruses are not eliminated efficiently and remain in the organism for a longer period of time. In addition, the virus has developed numerous strategies to escape the immune response (immune evasion). It is known that a persistent HPV infection can lead to disturbances in the cellular immune response and increase immune tolerance (e.g. via increased infiltration of regulatory T cells), which significantly favours the progression of cell changes[5]. The role of chronic inflammation in the development of HPV-associated cancers is also discussed in the literature[6].

Given the severe consequences of persistent infections, it is recommended to support the proper functioning of the immune system.

There is currently no allopathic treatment available for the elimination of HPV. However, immunotherapies open up promising prospects for the treatment of these infections and associated diseases[7].



1. HPV reaches the basement membrane of the multi-layered squamous epithelium via micro-lesions of the skin and mucous membrane and infects basal cells.
2. After primary infection, only a small amount of viral genomes and weak transcription of early genes E1, E2 and E5 are found in basal cells.
3. HPV-infected cells divide and migrate into the suprabasal layers. All early genes are expressed in the stratum spinosum and DNA replication begins, with a high amount of viral genomes present. The capsid proteins L1 and L2 are also synthesised and the assembly of new virus particles begins.
4. Mature, infectious virions are present in the stratum granulosum, which are released in the uppermost cell layer (stratum corneum in the skin) with exfoliating cells.

Fig. 1: Simplified scheme of the HPV replication cycle

The Micro-immunotherapy Approach in Anogenital HPV Infections

Micro-immunotherapy (low-dose immunotherapy), which draws from the natural functioning of the immune system, provides a valuable immunoregulatory treatment option in everyday practice (Fig. 2). The micro-immunotherapy formula PAPI is the treatment of choice for immune support in anogenital HPV infections and associated clinical pictures. The fields of application of this formula, which is composed of cytokines, cyclosporin A, ribonucleic acid and specific nucleic acids (SNA) in low doses (see Appendix 1), include anogenital condylomas and cervical dysplasia.

Note:

SNA®-PAPI is specifically directed against HPV types 6, 11, 16 and 18, although clinical experience shows that the PAPI formula can also be used successfully for other HPV types due to its complex composition.

For infections with HPV types that cause common skin warts, the formulas VERU or VERU-JUNIOR are used.

The recommended dosage is 1 capsule/day for a period of 3-6 months for anogenital condylomas and at least 6 months for cervical dysplasia. Treatment can also be continued for longer if the treating doctor/therapist deems it necessary. It is recommended that the partner is also treated.

If there is a risk of neoplasia (from PAP IV or CIN II / CIN III or HSIL) and in the case of carcinomas with confirmed HPV involvement, the formula PAPI (1 capsule/day) should be administered in combination with the formula C1 (immune support in case of solid tumours) (1 capsule/day) for at least 6 months. The two formulas should be taken approximately 2 hours apart.

What is micro-immunotherapy?

Micro-immunotherapy is an immunotherapy in which immunomodulatory substances (mainly cytokines) are used in low doses to restore or maintain the balance of the immune system through targeted, sequential information transmission. This approach takes into account natural processes and ensures good tolerability (Fig.2)

Fig.2: Mechanism of action of micro-immunotherapy formulas

The micro-immunotherapy formula PAPI is aimed at the following objectives (see Appendix 1):

- Block HPV proliferation and prevent infection of further cells
- Regulate immune function and dampen chronic inflammation promoting oncogenesis
- Prevent associated diseases

This treatment offers various advantages and represents a valuable support in daily clinical practice:

- In cases with unclear cytology or equivocal gynaecological findings, the watchful waiting strategy is applied until the next check-up. Existing values may improve or worsen in the further course. This waiting period can be very stressful for women. The micro-immunotherapy formula PAPI offers the opportunity to actively use the control period to promote the body‘s own defences and positively influence cell changes.

- Clinical experience shows that this treatment can usually improve the findings (lower level of PAP findings or normalisation) or counteract a possible progression of the cell changes. This can often save the patient from having to undergo conisation. This is, being particularly advantageous for women who wish to have children, as conisation increases the risk of infertility and premature births.

- The micro-immunotherapy formula PAPI is also a valuable option for patients with severe cell dysplasia (e.g. PAP IV A) who refuse conisation.

Studies

Several clinical studies on the use of micro-immunotherapy for anogenital HPV infections have been published in recent years.

The efficacy of the micro-immunotherapy formula 2LPAPI® was researched in 2016 in a prospective follow-up study by Thomas G. et al. The follow-up study involved 36 patients aged between 20 and 45 years who were HR-HPV carriers and had abnormal cytological findings of the ASCUS (atypical squamous cells of undetermined significance) or CIN I (cervical intraepithelial neoplasia grade I) type. The patients were allocated either to the medication group (2LPAPI®, 1 capsule/day over a period of 6 months) or to the control group (conventional monitoring without medication), depending on whether they wanted to be treated with the micro-immunotherapy formula or not. A total of 18 patients were included in each of the medication and control groups. The Pap smear and HPV test were checked after 6 and 12 months. After 12 months, the results showed complete HR-HPV clearance in 14 of the treated patients compared to 8 of the untreated patients (78% compared to 44%), although the difference was not statistically significant due to the small number of participants. However, in the subgroup of patients aged over 25, who are at higher risk of cervical cancer, a statistically significant HR-HPV clearance was achieved: 13 patients in the treatment group achieved complete viral clearance compared to 2 patients in the control group. In this age group, the micro-immunotherapy formula also had the strongest effect on cytological normalisation (regression from CIN I to ASCUS and from ASCUS to normal) and almost reached statistical significance compared to the control group[12].

Link to prospective follow-up study on 2LPAPI®

https://www.scirp.org/journal/paperinformation.aspx?paperid=64702

The clinical efficacy of 2LPAPI® was also evaluated in a study conducted by Milani G. in Italy in 2016. 32 patients between the ages of 22 and 60 took part, all of whom were HR-HPV positive (15 of whom tested positive for serotypes 16 and 18). They were treated for 2 months with 2LPAPI® (1 capsule/day) in combination with the preparation Galium-Heel (20 drops sublingually in the morning). After 3 months, viral clearance was observed in 26 of the treated patients (81.25 %)[13].

In 2012, Mazzoli S. et al. conducted a follow-up study of asymptomatic patients with a high-risk (HR) HPV infection (HR-HPV), which was confirmed by PCR testing. In this study, 31 patients were followed up in a private practice over a period of 2 years (2009-2010). 16 patients were treated with the micro-immunotherapy formula 2LPAPI® (1 capsule/day over a period of 4 months), while 15 received no treatment. At the end of the study period, HR-HPV clearance was observed in 50% (8/16) of treated patients compared to 7% (1/15) of untreated patients[14].

The results need to be confirmed in further clinical trials with a larger number of patients and a double-blind, placebo-controlled design.

Case Reports

Multiple condylomata acuminata

Dr Cristina Zemba *(Barcelona, Spain)*

This case concers a 28-year-old female patient with multiple condylomata acuminata on the labia minora and the clitoris. A year earlier she had suffered from genital warts and had undergone CO2 laser treatment. In the course of this treatment, she separated from her partner and was single for several months. After starting a new relationship, the genital warts recurred.

She is afraid to undergo laser treatment again due to the associated pain (especially in the clitoral area) and visits my practice in search of gentler methods. The patient is taking the contraceptive pill and her partner is not using a condom.

Both the patient and her partner are treated with the formula PAPI (1 capsule/day) for 4 months. In addition, the patient takes a vitamin B complex (1 x/day) and oral probiotics with L crispatus, L rhamnosus and L gasseri (1 x/day).

After 4 months, lesions have reduced to 3. Treatment with the formula PAPI (1 capsule/day) is continued for an additional 2 months. Co-treatment of the partner is discontinued. 2 months later the genital warts are fully gone.

Practical tip:

It is recommended that the partner is also treated with micro-immunotherapy.

Practical tip:

Micro-immunotherapy can be combined synergistically with other treatment approaches such as micronutrient medicine or microbiological therapy.

Cytological smear with ASCUS result

Dr Diego Jacques Grauwet *(Madrid, Spain)*

The patient is a 32-year-old woman with an ASCUS cytological smear and a positive HPV test for high-risk types 16, 18 and 45. Treatment with the formula PAPI (1 capsule/day) is prescribed for 6 months. After 8 months, the follow-up examination shows normal smear results and the HPV test is negative.

Cytological smear with ASC-H result

Dr Diego Jacques Grauwet *(Madrid, Spain)*

In July 2017, the cytological examination of a 34-year-old, non-smoking patient revealed ASC-H (atypical squamous cells, cannot exclude HSIL) and positive serology for HPV33. The biopsy performed shows a CIN II (cervical intraepithelial neoplasia grade II) result. She also reported that she had used the contraceptive Yasmin continuously between 2010 and 2013.

Treatment is initiated with the formula PAPI (1 capsule/day) for 6 months in combination with the formula C1 (1 capsule/day) for 4 months. In addition, a homoeopathic drainage of Yasmin is carried out.

At the follow-up visit in February 2018, test results were as follows: normal and unsuspicious findings in the cytology and biopsy as well as negative HPV diagnostics using PCR.

Practical tip:

In the case of severe dysplasia, it is recommended to administer the formula PAPI in combination with the formula C1.

Cytological smear with CIN I result

Dr Victoria Motger *(Barcelona, Spain)*

In March 2017, a 30-year-old woman visits my practice for the first time. She reports that she had undergone an annual cytological examination in February, which revealed findings of type CIN I with pronounced inflammatory changes. At that time, she was prescribed the tetravalent HPV vaccine and administered the first dose. Her mother - a former patient of mine - referred her to my practice to get a second opinion.

The patient, who has a degree in a health-related field, receives information on the subject and decides not to follow the recommendations to administer the two remaining doses of the vaccine. Treatment is initiated with the micro-immunotherapy formula PAPI (1 capsule/day) and homeopathic suppositories (1 dose at the end of each menstrual period). Selenium is also administered to boost immunity.

Note:

The micro-immunotherapy formula PAPI is used to treat HPV infections. HPV vaccination is designed as a prophylaxis. A decision on vaccination should always be made together with the treating doctor/therapist and the patient.

In June 2017, a follow-up examination is performed. Results are normal and show no evidence of inflammatory changes. The patient therefore discontinues the previous treatment.

In March 2018, a new cytological examination reveals LSIL (low-grade squamous intraepithelial lesion), so treatment with the PAPI formula is resumed. In addition, serological tests for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are run in order to rule out the possible influence of these viruses. Test results are, however, unremarkable in this case. It should also be mentioned that the patient was harassed at work between the end of 2017 and the beginning of 2018, was dismissed due to depression and filed a complaint against the person who had exposed her to this harassment. At the check-up in June 2018, she is found to have ASCUS. She is recommended to continue treatment with the formula PAPI.

Practical tip:

In the case of treatment blockages with the formula PAPI or more complex cases, herpes viruses such as EBV or CMV should be checked serologically and treated with the corresponding micro-immunotherapy formulas if the findings are conspicuous, in order to positively influence the course of treatment.

Cervical and vulvar dysplasia

Dr Ina Chammah *(Brunswick, Germany)*

Patient case

A 65-year-old female patient visits my practice in August 2019 with the following findings:

- Dysplasia in the vulvar area
- Vulvar histology precancerous stage VIN II; high-grade squamous intraepithelial lesion VIN II
- Cervical histology: PAP2
- HPV test: HPV-16+

Lymphocyte typing - August 2019

Due to the severity of the case, lymphocyte typing (Fig. 3) is performed in order to determine the immune status and adapt the treatment accordingly. It shows non-adaptation with lymphopenia (decreased total number of lymphocytes).

T4 cells are increased and T8 cells are decreased. Increased values of TH17 cells are also conspicuous, indicating an increased propensity for inflammation.

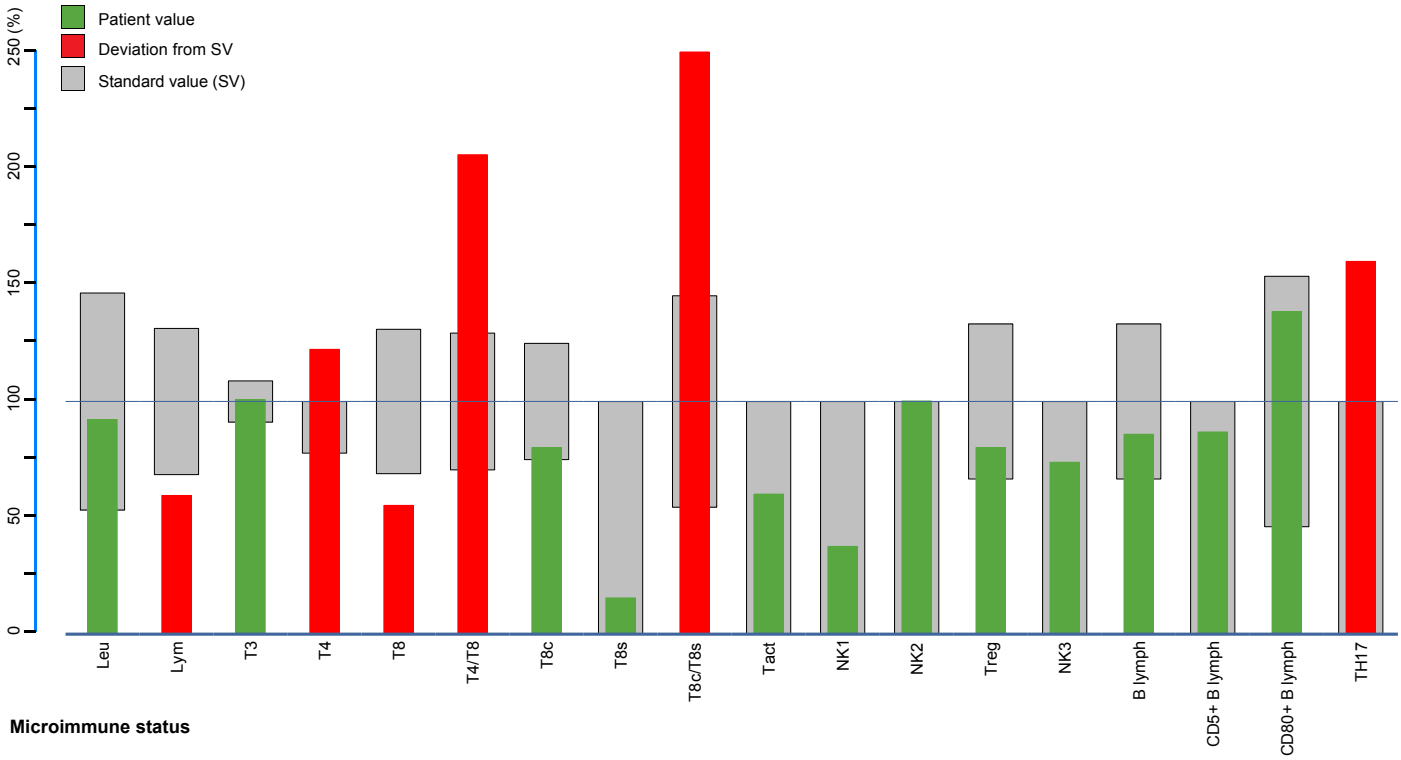


Fig. 3: Lymphocyte typing (August 2019)

Treatment - August 2019

The formula PAPI is administered in combination with the formula EID (general immune support) (1 capsule/day with at least two hours between intakes).

The following preparations are also administered:

- 3x administration of Thuja C200 within 6 months (homoeopathic treatment for dysplasia and condyloma)
- Vitamin C (3x 1000 mg/day)
- Ovula vitamin D (3x 10,000 I.U/week)
- Symbiovag suppositories (3x/week)
- Omega 3 (1500 mg/day: 707 mg EPA, 368 mg DHA and 84 mg DPA)

Practical tip:

The formula PAPI can be easily used in daily practice on the basis of the patient's clinic and the PAP findings or the HPV test - without further laboratory tests. In more complex cases, it may prove helpful to perform lymphocyte typing to determine the immune status. In cases of non-adaptation with lymphopenia/hyporeactivity, the formula PAPI can be combined with the formula EID for 4-6 months or longer if necessary.

- In the case of non-adaptation with lymphocytosis/hyperreactivity, the formula PAPI is combined with the formula EAI for 1-2 months and then with the formula EID for a further 2-4 months.

Follow-up - December 2019

At the follow-up examination, both cervical and vulvar smears show PAP1 (last time it was PAP2).

Treatment with micro-immunotherapy is continued:

- Formula EID (1 capsule/day)
- Formula PAPI (1 capsule/day)

Follow-up - February 2020

The dysplasia examination is without findings and the smear test shows PAP1.

As the patient has a new partner, treatment is continued at a reduced dose to counteract possible reinfection:

- Formula PAPI (1 capsule/day) and formula EID (1 capsule/day) in an alternating 10-day rhythm.

Follow-up - February 2021

In the further course there are no pathological findings. The formula EID is discontinued and the formula PAPI (1 capsule/day according to the following regime: intake for 10 days - 20 days break) is administered until summer 2021. Treatment is then discontinued.

Note:

The usual duration of treatment with the formula PAPI for dysplasia is at least 6 months. In this case, however, treatment was given over a longer period due to the severity of the findings and the new partner.

Testimonials

Dr Diego Jacques Grauwet (Madrid, Spain)

In my daily practice, micro-immunotherapy is a valuable treatment approach and my first choice for viral infections in the genital area, significantly improving the quality of life of my patients.

Dr Victoria Motger (Barcelona, Spain)

When I first came across micro-immunotherapy, I had already 30 years of experience as a practising specialist in obstetrics and gynaecology. More than once I had to suggest a treatment such as cervical conisation to young women, some of whom had not yet had children. Several of them had complications from the second trimester onwards with the associated consequences, including complete bed rest, imminent premature labour or rupture of the membranes.

Since I started using micro-immunotherapy for HPV-associated lesions, I have been able to reverse the premalignant cell changes in most cases, thereby improving prognosis for patients. I have also realised that co-infections with viruses such as the Epstein-Barr virus can influence the further course of the disease. For this reason, I usually combine the formula PAPI with the formula EBV in patients who do not respond appropriately to the initiated therapy, if a corresponding serological burden is detected.

Dr Ina Chammah (Brunswick, Germany)

I have yet to have a patient whom the formula PAPI has not helped, always achieving safe and fast results. Neither have colleagues of mine had any treatment failures with this treatment. I therefore recommend micro-immunotherapy to all doctors and therapists as the first therapeutic measure for anogenital HPV infections.

Conclusion

Micro-immunotherapy is a valuable and safe treatment option for HPV infections in the anogenital area and associated diseases, which can be prescribed without hesitation in everyday practice. Micro-immunotherapy can be a great help, especially for patients whose chances of spontaneous healing of the HPV infection decrease with increasing age (approx. from the age of 25). Experience has shown that in most cases, supporting the immune system leads to a regression of the cell changes associated with this virus and surgical interventions can be prevented. Men infected with HPV can also benefit from micro-immunotherapy.

Appendix 1: Immunoregulatory objectives of the formula PAPI

The micro-immunotherapy formula PAPI is composed of a specific combination of immunomodulatory substances in low doses (LD) & ultra-low doses (ULD). This formula, which is used for HPV infections and associated diseases, is aimed at exerting an effect on the overall system with multiple objectives (Fig. 4 and 5).

In the following, the mechanism of action of the formula PAPI is described in more detail.

HPV life cycle

- **Block HPV proliferation and prevent infection of further cells**
  - The specific nucleic acid SNA®-PAPI used in the formula PAPI in ULD is directed against these viruses.
  - The use of cyclosporin A (CsA) in ULD is aimed at modulating the p21 signalling pathway and inhibiting increased proliferation of infected cells.
  - Interleukin 1 (IL-1) in ULD aims to reduce the proliferation of keratinocytes.

Immune response to HPV

- **Regulate immune function and dampen chronic inflammation promoting oncogenesis**
  - The aim of using ribonucleic acid (RNA) in ULD is to prevent excessive activation of toll-like receptors and to dampen the inflammatory response.
  - The use of CsA in ULD aims to counteract the inhibitory effects of this substance on the differentiation of Langerhans cell precursors in the epidermis and thereby promote antigen presentation.

- Interleukin 2 (IL-2) in ULD is aimed at counteracting immune tolerance and virus persistence and favouring the immune response.

HPV-associated diseases

Prevent associated diseases

- The use of interferon alpha (IFN-α) in ULD aims to inhibit the expression of the viral oncogenes E6 and E7 by inhibiting the transition from the episomal to the integrated form of HR-HPV.
- The use of SNA®-HLA II in ULD is aimed at counteracting the expression of the HLA-DR molecules in non-professional antigen-presenting cells (APC) (including keratinocytes) and thus the development of cervical cancer.

The active ingredients contained in the micro-immunotherapy formulas are processed according to a specific preparation mode called "Serial Kinetic Process" (SKP). It consists of a 1:100 serial dilution process, followed by a vertical shaking. These steps undergo a predetermined number of repetitions. Depending on the preparation, the effect of the substances may vary[5-8].

The active ingredients used in LD aim to upregulate the activity of the substance in the organism according to its natural physiological effect (shown in green in Fig. 2). In contrast, the substances used in ULD are designed to modulate or maintain (shown in blue) or downregulate (shown in red) the activity of the substance in the organism [8-11].

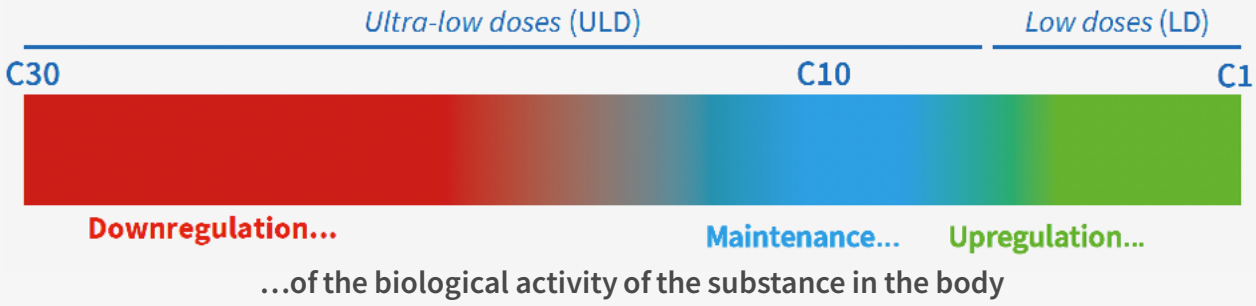


Fig. 4: Objectives of the active ingredients contained in the micro-immunotherapy formulas depending on their preparation mode.

There is an extensive literature that describes the reversal of the effect of immunomodulatory substances and other stimuli, depending on the applied dosage. This phenomenon is called hormesis and refers to an adaptive response that is triggered by weak stimuli in the organism to optimise its functioning and resistance to greater stress[9-10]. This biological phenomenon of hormesis could provide an explanation for the functioning of LD & ULD used in micro-immunotherapy[5-8].

Link to the complete description of the model of the mechanism of action of the formula PAPI

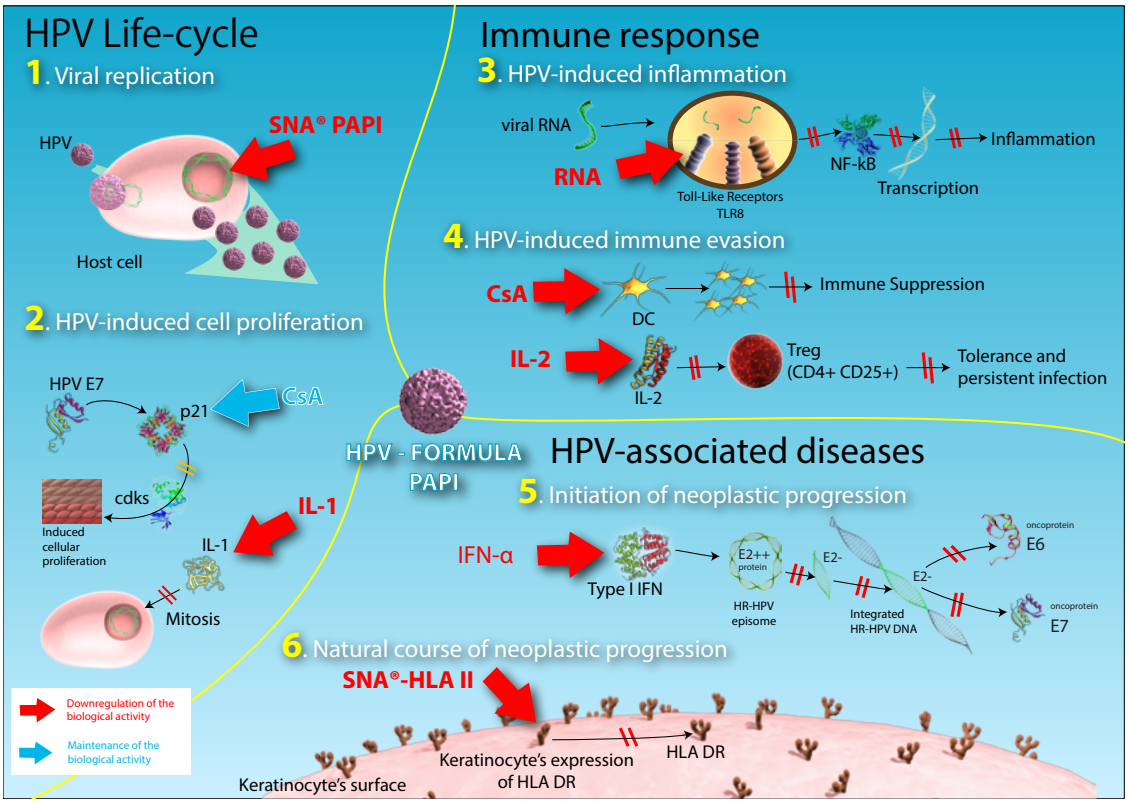


Fig. 5: Immunoregulatory objectives of the micro-immunotherapy formula PAPI

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