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REVIEW

A Review on Inosine Pranobex Immunotherapy for Cervical HPV-Positive Patients

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Abstract: The purpose of this review was to examine and summarize data for inosine pranobex (IP) immunotherapy in cervical HPV-positive patients. Persistent or recurring cervical human papillomavirus (HPV) infection is a major cause of cervical cancer. Self-clearance and blocking of cervical HPV infection depend on the status of the host immune system. Immunotherapy helps accelerate elimination of the infection. Host immunity is involved in the development of HPV infection. Several mechanisms of interaction between the virus and the immune system have been revealed; however, the mechanisms have not been completely elucidated. A properly functioning immune system impedes HPV progress and helps clear the pathogen from the body. IP has antiviral efficacy because it modulates both cellular and humoral immunities. IP has been on the market since 1971. Nevertheless, it has seldom been administered to treat cervical HPV infections. In this review, Google Scholar, PubMed/MEDLINE, Scopus, Cochrane Library, and Research Gate were searched for the period 1971–2021. Prospective controlled trials, observational and retrospective studies, and meta-analysis and reviews on immunotherapy against HPV cervical infection were explored. Prior studies showed strong clinical efficacy of combined and standalone IP therapy in reversing HPV-induced changes in the cervix, preventing disease progression, and clearing the pathogen. IP treatment enhanced host antiviral activity against HPV, delayed or stopped cervical oncogenesis, and rapidly removed HPV from the body.

Keywords: cervical neoplasia, clearance, humoral immunity, innate immunity, oncogenesis, inosine pranobex

Introduction

To date, >200 human papillomavirus (HPV) types have been detected.[1–3] The most common HPV transmission route is sexual contact.[2] Sexually active individuals will acquire ≥ 1 anogenital HPV genotype at some point in their lives.[4] Sensitive PCR monitoring has indicated that most HPV infections are cleared by the immune system and disappear within 1–2 y without clinical complications.[5,6] Epidemiological evidence for HPV carcinogenicity was first presented by zurHausen in 1983 and accepted in 1995 by the International Agency for Cancer Research (IARC) of the World Health Organization (WHO).[4] HPV carcinogenicity was first established for cervical precancers and cancers. Cervical carcinogenesis is a multi-step process starting with HPV infection of the cervical epithelium. However, cancer onset occurs after persistent or recurring HPV infection.[7] There is ample evidence to support the hypothesis that host immunological status and HPV-induced immune changes are responsible for persistent HPV infection and subsequent development of cervical neoplasia.[7–9]

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The immune system eliminates the virus and recognizes the tumor antigen associated with cervical carcinogenesis.[7,9] Both cellular and humoral immunity are vital for clearing cervical HPV infection.[8,9]

To date, no antiviral drugs effectively kill or hinder the progress of cervical HPV.[10] Hence, host immunity alone must fend off and clear genital HPV.[11] However, the host immune response may be inadequate and require modulation.[12] Suppressive modulations may be required when the host immune response is too strong. In contrast, immunostimulation is needed when host immunity is weak.[12]

Immunotherapy is an essential treatment modality for microbial infections, malignancies, and other forms of pathogenesis.[13] Immunotherapeutic agents may be specific and nonspecific.[14] Immunomodulators are nonspecific immunotherapeutic agents and can be immunostimulants or immunosuppressants.[15] The former induce nonspecific humoral and cellular immune responses.

Inosine pranobex (IP), also known as inosine acedobendimepranol (INN) or methisoprinol, is an antiviral drug consisting of a 1:3 ratio of inosine and dimepranolacedoben. The latter is a salt of acetamidobenzoic acid and dimethylaminoisopropanol.[16] Since 1971, IP has been licensed for the treatment of cell-mediated immunodeficiency associated with human papillomavirus (HPV), herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV).[16]

The purpose of this review was to examine and summarize data on IP immunotherapy for cervical HPV-positive patients.

Materials and Methods

Google Scholar, PubMed/MEDLINE, Scopus, Cochrane Library, Research Gate, were searched from 1971 when IP was first licensed until 2021. The main terms used during database search were cervical human papillomavirus infection, clearance, persistence, oncogenesis, immunity, inosine pranobex, and immunomodulation.

Prospective controlled trials, observational and retrospective studies, meta-analysis, and reviews on immunotherapy against HPV cervical infection were examined. The primary outcomes were persistence and clearance of cervical HPV genotypes in women undergoing IP therapy and the onset of low- or high-grade cervical intraepithelial neoplasia (CIN) or LSIL/HSIL (low/high squamous intraepithelial lesions) in patients being monitored for a certain period of time. The overall quality of evidence for immunotherapy against cervical HPV infection was evaluated. Of 108 identified abstracts, 62 full-text articles were reviewed, and 41 studies were included in the synthesis.

Cervical HPV Infection: Self-Clearance and Persistence

Persistence of HPV infection is critical in the development of cervical precancerous lesions and cancer. The main unresolved issues regarding the natural history of HPV are the extent to which the viral infection is self-cleared and the time required for this process.[17] Unlike self-clearance, persistence, or the time during which HPV infection remains detectable, is unclear.[17,18] Persistence is longer for high-risk than low-risk HPV types.[5,19,20] Only ~10% of all HPV infections persisting for several years were strongly associated with a high absolute risk of a precancer diagnosis.[21–23]

Rositch et al[24] carried out a meta-analysis of published studies on the persistence and self-clearing of HPV infection and the risks of developing CIN and cervical cancer associated with it.[24] They summarized the data for 86 studies involving > 100,000 patients.[24] The authors concluded that ~50% of the HPV infections persisted within the last 6–12 mo.[24] Cervical HPV tests at 12-mo intervals can identify women at an increased risk of high-grade CIN as a result of persistent HPV infection.[24] The PATRICIA study comprised 4825 women with cervical HPV infections.[25] The aim of that trial was to determine the proportions of HPV infections that are cleared or progress to CIN.[25] Persistent infection with high-risk HPV genotypes more frequently leads to CIN compared to persistent infections with low-risk HPV genotypes.[25] High-risk HPV type infections were the least likely to be cleared.[25] Miranda et al[26] surveyed 569 women in Brazil for persistence and clearance of HPV infection over 24 mo. Eighty-nine of these patients were HPV positive.[26] After 24 mo, HPV persistence and clearance were observed in 59.6% and 40.4% of the women, respectively.[26] High-risk HPV genotypes persist over a longer period of time and play a major role in CIN and cervical cancer pathogenesis.[26]

Cervical HPV clearance and persistence depend on host immunity.[7,27–30] Adequate immune response is vital to the self-clearance of numerous cervical HPV types.[27,28,30] Ineffective immune response is associated with insufficient activation of congenital immunity, non-inclusion of the adaptive immune response, or strong viral persistence.[7,29,31,32] Nguyen et al followed systemic and

mucosal immune responses to cervical HPV in women who underwent radical hysterectomy for cervical cancer (HCC) or loop conization for cervical dysplasia.[8] They analyzed HPV-specific antibodies through ELISA and cytokine assays performed with the Linco cytokine multiplex method using Luminex technology on vaginal washes.[8] They found relatively lower levels of HPV16 E7-specific immunoglobulin A (IgA) in the vaginal wash of women with cervical cancer and cervical dysplasia compared with the control. Neither Th1-nor Th2-type cytokine induction was detected in the cervical cancer group.[8] Thus, selective downregulation of local HPV-specific IgA responses occurred in the cervical cancer patients.[8]

In HPV-induced carcinogenesis, interactions between virally infected keratinocytes and the cervical local immune response can determine the course of the disease.[30] Elucidating these interactions could help develop innovative diagnostic immune tests to determine cervical pre-cancer progression and design novel immunotherapy approaches targeting the mechanisms and pathways involved in HPV-induced carcinogenicity.[30]

Cervical HPV Infection and Host Immune Response

HPV is an epitheliotropic virus that exclusively attacks epithelial cells and primarily spreads and acts locally in this type of tissue. In the cervix, HPV infects the keratinocytes in the basal layer of the cervical epithelium in the transformation zone of the cervix.[27,30,33,34] Viral replications markedly increase in differentiated epithelial layers that have undergone recent desquamation.[27,35] Viral particles are assembled when differentiated keratinocytes die and the virus is released during desquamation into the ambient environment.[35] Downregulated protein expression in the lower epithelial layers, high non-cytolytic genomic replication, and the absence of a viremic phase enable the virus to evade immune system recognition.[33,34]

Keratinocytes infected by HPV initiate an adaptive immune response[36] as they are part of innate immunity. Antigens may not be fully represented in keratinocytes but the cells nonetheless upregulate the cytokines TH1 and TH2 and cytotoxic responses in $CD4^+$ and $CD8^+$ memory T cells, respectively.[7,30,36] $CD4^+$ T helper (Th1 and Th2) and $CD8^+$ T cell responses were identified in patients with genital HPV-induced warts.[37] Comparisons of HPV6 and HPV11 antigen-specific T cell responses between venereal wart patients and healthy controls disclosed low frequencies of IFN-γ-producing $CD4^+$ and $CD8^+$ T cells in HPV-infected women.[37] The relative number of IL-4-expressing $CD4^+$ T cells was significantly higher in infected women than in normal women.[37] The observed change from Th1 to Th2 in HPV-infected patients was a consequence of a weakened immune response caused by the HPV infection. A direct effect of depressed CD8 T cell activity is delayed or poor genital wart clearing.[37] In the female genital tract, keratinocytes express several Toll-like receptors (TLR) on the cell surfaces (TLR-1, TLR-2, TLR-4, TLR-5, and TLR-6) and in the endosomes (TLR-3 and TLR-9).[7,30,38] TLR are a family of immunological receptors that recognize pathogen-related molecular patterns (PAMPs) and induce congenital and adaptive immune responses.[7,28] TLRs recognize viral nucleic acids. TLR-3 recognizes one-sided-chain RNA (dsRNA) while TLR-7 and TLR-8 recognize single-chain RNA (ssRNA) and TLR-9 recognizes CGG-rich DNA.[28] Activated TLRs receptors induce cytokine production and strong anti-inflammatory responses.[39] Switching on TLR-9 in keratinocytes initiates the production of TNF-α, IL-8, CCL2, CCL20, CXCL9, and type 1 IFN.[40,41] The second level is adaptive immunity via cytotoxic T lymphocytes (CTLs) targeting HPVE2 and HPVE6 and eliminating HPV-infected cells.[41] $CD4^+$ and $CD8^+$T lymphocytes predominate in cervical epithelium.[33] Langerhans cells are located on the surface epithelial layers.[33] When HPV attacks the epithelium, Langerhans cells switch on and activate T lymphocytes.[42] Adequate T cell immune responses regress HPV-induced lesions and clear local HPV infection.[43] Inactive T cell immune responses are associated with long-term viral persistence and cervical cancer induction.[33]

HPV can evade encounters with the immune system.[28,33,41] As HPV lacks a viremic phase, immune cells cannot easily enter into contact with it.[28,33] HPV attacks basal epithelial layers of the cervix as immunocompetent Langerhans cells occur only in the surface epithelial layers and avoid invoking the T cell immune response.[33,44] HPV does not cytolyse the cervical epithelium. In this way, it attenuates inflammatory and immune signal responses and can persist incognito.[41,44] HPV also avoids the immune response by downregulating its oncogenes throughout the initial life cycle and only synthesizing immunogens such as L1 and L2 capsid proteins in surface epithelial layers that undergo desquamation.[33,34,41]

Evasion of a local immune response is required for the development of successful cervical HPV infection.[33,44] Therefore, the application of therapeutic agents stimulating innate immunity may effectively prevent the onset of local HPV infections.

Inosine Pranobex: Immunomodulatory Mechanism

Inosine acedobendimepranol (IAD) is a synthetic purine derivative consisting of a 3:1 ratio of *p*-acetamidobenzoic acid salt of N,*N*-dimethyl-amino-2-propanol (DiP.PAcBA) and the β polymorph of the β anomer of inosine.IAD has immunomodulatory and antiviral properties[15] and is registered in numerous countries under the brand names Immunovir, Isoprinosine, Viruxan, Inosiplex, Methisoprinol, and Inosine Pranobex.[15]

IP was introduced in 1971 and several studies from the 1970s and 1980s showed that it did not induce serious side effects and was well tolerated by patients.[45,46] At high doses and after long-term use, the metabolites of IP may cause reversible increases in serum urinary uric acid and nausea.[45,46]

Several studies have demonstrated that IP is antiviral and immunomodulatory. However, its exact mechanisms are not fully understood.[47] IP affects cellular and humoral immunity and is antiviral by immunomodulation.[47]

IP stimulates a Th1 cell response characterized by proinflammatory cytokine (IL-2 and IFN-c) upregulation in mitogen- and antigen-activated cells.[48,49] Induction of IL-2 and IFN-c activates T lymphocyte maturation and differentiation and the lymphoproliferative response.[49,50] Similarly, IP modulates T lymphocyte and natural killer cell cytotoxicity and T8 suppressor and T4 helper cell function and increases the numbers of immunoglobulin G (IgG) and complement-surface markers.[47] Certain studies investigated the influences of IP on Th1- and Th2-related cytokines. When the lymphocytes were at rest, the cytokine levels remained constant.[49,51] Lymphocyte stimulation with IP upregulated IL-2, interferon c (IFN-c),and tumor necrosis factor alpha (TNF-a) and downregulated IL-4, IL-5, and IL-10.[49,51]

IFN-c expression and IP block IL-10 production. Moreover, IP downregulates other anti-inflammatory cytokines and may block their effects on the immune response.[52] IP administration increases the number and activity of natural killer cells (NK).[47,53] NK activity in eosinophils rises in response to increases in the numbers of lgG and complement-surface markers as well as macrophage, monocyte, and neutrophil chemotaxis and phagocytosis.[51,53]

IP suppresses the synthesis and translational ability of lymphocyte mRNA and inhibits viral RNA synthesis by:

1) inosine-mediated inclusion of orotic acid in polyribosomes;
2) suppression of polyadenylic acid capture by viral mRNA; and
3) molecular reorganization and a nearly threefold increase in the density of intramembrane plasma particles (IMP).[54]

The humoral immune response consists of activating B lymphocyte transformation into plasma cells and initiating antibody production.[55] B lymphocyte transformation may be a response to IP action but also a consequence of the effects of IP on macrophages and T helper cells.[47] IP stimulates certain immune mediators, promotes Th1 cells, and inhibits Th2 cells.[50] Most of the 21 healthy patients undergoing daily administration of 4 g IP in a Bulgarian study presented with rapid immune responses, increases in the numbers of their lymphocytes, and circadian fluctuation of these parameters in their peripheral blood.[56] In another Bulgarian study, serum cytokine levels were measured in 10 healthy volunteers during and after IP treatment (1 g IP, 3x daily, 3 wks).[48] Increases in proinflammatory cytokine levels were observed.[48] Another trial evaluated lymphocyte subsets [$CD19^+$ B cells, $CD3^+$ T cells, $CD4^+$ T helper cells, FoxP3hi/CD25hi/CD127lo regulatory T cells (Tregs), CD3-/$CD56^+$ NK cells, and $CD3^+$/$CD56^+$ NKT cells], serum immunoglobulins, and IgG subclasses in ten healthy volunteers being administered 4 g IP daily for 14 d.[15] NK cell counts increased over time and recurred at the end of the study. Furthermore, different high/low Treg and T helper fractions were detected during the study period.[15]

The effects of IP on the immune systems of patients with different diseases were also investigated. Herpes virus-infected patients had higher lymphocyte transformation rates than healthy controls.[57] In patients with autoimmune diseases and chronic active hepatitis B, IP therapy increased the numbers of active T cell rosettes and enhanced responses to mitogen activation.[58,59] High NK cell activity and elevated numbers of $CD4^+$ T helper cells were observed in patients with chronic fatigue syndrome undergoing IP therapy.[60]

Despite the foregoing studies and their findings, the precise immunomodulatory mechanism of IP remains to be clarified.

Cervical HPV Infection and IP Immunotherapy

The first studies on IP administration to patients with genital HPV infection were published in the 1970s and 1980s soon after the drug was launched. Most reports evaluated the clinical efficacy of IP combined with cryotherapy, surgery, or electrosurgery of genital condylomata. In most cases, clinical efficacy of the combination therapies surpassed that of IP administration alone. Sadoul and Beuret followed two groups of patients with cervical or vulvovaginal condylomata.[61] They were treated either with CO_2 laser or with CO_2 laser plus IP.[61] Monotherapy was less efficacious than the combination treatments.[61] Combination therapy consisting of CO_2 laser plus IP significantly reduced the number of recurring condyloma acuminate.[61] Mohanty and Scott compared the efficacies of IP, conventional therapy, and their combinations in 165 patients with genital warts.[62] Whereas conventional therapy alone had 41% efficacy, the combination of IP plus conventional therapy increased efficacy to 94%.[62] The patients undergoing IP therapy in this study presented with relatively higher numbers of B cells.[62] In a multicenter, prospective, randomized, placebo-controlled study, Davidson-Parker et al administered 3 g IP daily for 4 wks to 55 patients with genital warts.[63] The IP therapy improved the relative clinical efficacy of the conventional treatment (podophyllin or trichloroacetic acid).[63] Nejmark et al evaluated the efficacy of combination therapy including IP for the treatment of male genital warts.[64] The combination therapy had long-term efficacy and there was only a 7% relapse rate. In contrast, destructive therapy was associated with a 32% relapse rate.[64] The authors recommended IP (isoprinosine) for both the complex therapy and prevention of the recurrence of genital warts.[64] Tay performed a randomized, placebo-controlled study on the efficacy of IP immunotherapy. They orally administered 1 g IP thrice daily for 6 wks to 55 patients with vulvar HPV infections. There were 22 patients in the IP group and 24 in the placebo group.[65] After 2 mo, IP monotherapy proved effective in 14 (63.5%) of the patients. However, only 4 patients (16.7%) in the placebo group presented with substantial improvement in vulvar epithelial morphology ($P = 0.005$).[65] The authors concluded that IP therapy is suitable for the treatment of vulvar HPV infections.[65]

IP has been on the market since 1971.Nevertheless, our scientific literature and electronic databases searches revealed that only a few studies mainly from the last 20 y have focused on the use of IP in the treatment of patients with cervical HPV infections. It was only in 1983 that zurHausen discovered the connection between cervical HPV infection and carcinogenesis. Moreover, this finding was only accepted as irrefutable scientific fact by the global medical community in the 1990s. It has not been determined why IP immunotherapy has seldom been applied in the treatment of cervical HPV. Furthermore, some of the carcinogenetic mechanisms of HPV have been explored but there are some details that need to be completely clarified. Finally, the relationships among cervical HPV infection, host immune response, and the immune system remain to be established. For these reasons, IP immunotherapy has not been entirely adopted for the treatment of cervical HPV infection.

Most studies on IP administration for cervical HPV infection originated in Eastern Europe, especially Russia.[10,66–70] It appears that IP administration for immunotherapy against viral diseases is widespread and common in Eastern European countries. Table 1 provides a summary of the studies on the efficacy of IP in HPV genital infections.

Bitsadze et al reported that combined therapy including IP eliminated HPV in 98% of all cases and lowered the relative relapse rate by threefold.[68] Rakhmatulina reviewed numerous Russian studies and concluded that IP against HPV infection had 87.5–97% clinical efficacy in combination therapy and 72.4–95% clinical efficacy in monotherapy.[66]

Eliseeva et al assessed 5650 women with genital HPV infection from 33 towns in the Russian Federation before and after IP monotherapy and combined treatments.[71] After 6 mo, HPV self-clearance without treatment had occurred in 22.6% of all cases.[71] The rates of HPV negative cases were 35.5%,54.8%, and 84.2% after conventional, single IP, and combined IP treatments, respectively.[71] Therefore, combined IP had the greatest efficacy in terms of clearing genital HPV infection and regressing its associated diseases.[71] Pestrikova and Pushkar evaluated the effectiveness of IP treatment in 123 patients with cervical HPV pathology. HPV16 and HPV18 were the most frequently isolated viral types in this study.[72] IP treatment stopped CIN1 progression in 96.23±2.62% of all patients.[72] Cervical HPV clearance and full recovery were observed in 91.06% of all patients administered IP.[72] Pestrikova et al used colposcopy and PAP and cervical PCR tests for HPV16, 18, 31, 33, 35, 39,

Table 1 Summary of Studies Investigating the Efficacy of IP Therapy in HPV Genital Infections, Especially Cervical Infections

HPV Infection	Therapeutic Scheme	IP Treatment Duration and Dose Regimes	№ of Patients	Age	Follow Up
Genital warts[61]	CO_2 laser or CO_2 laser plus IP	–	–	–	–
Main findings[61] Monotherapy was less efficacious than the combination treatments.[61] Combination therapy consisting of CO_2 laser plus isoprinosine significantly reduced the number of recurring condyloma acuminate.[61]					
Genital warts[62]	Conventional treatment Conventional treatment plus IP therapy	One gram IP three times daily by mouth for four weeks	165 patients: 85 men/80 women	21–22 years	At 6 and 8 weeks and hereafter every four weeks, up to 24 weeks.
Main findings[62] Conventional therapy alone had 41% efficacy, the combination of IP plus conventional therapy increased efficacy to 94%.[62]					
Genital warts[63]	Conventional treatment (podophyllin or trichloroacetic acid) plus IP	4 week course of inosine pranobex 3 g a day	55	Over 18 years	At 8 and 12 weeks from entering the study
Main findings[63] The IP therapy improved the relative clinical efficacy of the conventional treatment (podophyllin or trichloroacetic acid).[63]					
Genital warts[64]	Destructive methods alone and with IP combination	IP- 3 g a day	-	20–30 years	8 month
Main findings[64] The combination therapy had long-term efficacy and there was only a 7% relapse rate. In contrast, destructive therapy was associated with a 32% relapse rate.[64]					
Vulvar HPV infection[65]	IP therapy alone and placebo	1 g IP thrice daily for 6 weeks	55	-	2 month
Main findings.[65] IP monotherapy proved effective in 14 (63.5%) of the patients. However, only 4 patients (16.7%) in the placebo group presented with substantial improvement in vulvar epithelial morphology (P = 0.005).65 The authors concluded that IP therapy is suitable for the treatment of vulvar HPV infections.[65]					
Genital HPV infection[71]	IP monotherapy and combined treatments	IP dose of 50 mg/kg of body weight for 10 days as a monotherapy or in combination	5.650	Under 20 years - over 66 years	6 months
Main findings[71] HPV self-clearance without treatment had occurred in 22.6% of all cases.[71] The rates of HPV negative cases were 35.5%, 54.8%, and 84.2% after conventional, single IP, and combined IP treatments, respectively.[71]					
Cervical HPV infection[72]	IP monotherapy	50 mg/kg per day thrice daily for 10 d, a break for 10 d, and later 2 more 10 d courses	123	20–80 years	6 months
Main findings[72] IP treatment stopped CIN1 progression in 96.23 ± 2.62% of all patients.[72] Cervical HPV clearance and full recovery were observed in 91.06% of all patients administered IP.[72]					

(*Continued*)

Table 1 (Continued).

HPV Infection	Therapeutic Scheme	IP Treatment Duration and Dose Regimes	№ of Patients	Age	Follow Up
Cervical HPV infection[73]	IP monotherapy	Three courses of 3000 mg IP daily at 10 d intervals between courses.	39	18–35 years	6 months
Main findings[73] At the end of the trial, viral load declined to a clinically insignificant level in 17.95% of all women and there was 74.36% cervical HPV clearance.[73]					
Cervical HPV infection and dysplasia[74]	Radio-wave conization and IP therapy	Three courses of 1.000 mg IP thrice daily for 10 d with 14 d intervals between courses	80	19–47 years	6 months
Main findings[74] At the end of the study, clearance of cervical HPV infection was confirmed for 97.5% of all patients.[74]					
Cervical HPV infection[67]	Electro-ablation plus IP therapy and IP monotherapy	1000 mg oral IP monotherapy thrice daily - 10 d	100	19–35 y.	60 days and 6 months
Main findings[67] Cervical HPV PCR revealed 88% clearance of cervical HPV infection at IP monotherapy group after 6 mo.[67] In the II group, the combined treatment provided 93.5% cervical HPV clearance after 6 mo.[67]					
Cervical HPV 16, HPV 18 infection[75]	IP monotherapy	IP – 1g tid., 10 days	45	32.2 ± 2.7 years	6 months
Main findings[75] Following a course of IP treatment: HPV 16 and 18 were undetectable in 77.8% and 50% of treated patients.[75]					
Cervical HPV infection[76]	IP monotherapy (I, II groups) and no therapy (III group)	Six 0.500-mg IP tablets taken at 8-h intervalsfor 14 (II group) and 28 (I group) days	125	32.2 ± 2.7	6 months
Main findings[76] After 6 mo, there was no evidence of cervical HPV infection in 93.7%, 78.0%, and 43.6% of the women in the first, second, and third groups, respectively.[76]					
Cervical HPV infection and HSIL[11]	Electroconization and electroconization plus IP therapy	1 g IP thrice daily at 8-h intervals for 1 mo. For the next 5 mo, 500 mg IP thrice daily at 8-h intervals	32	16 to 55 years	24 and 48 months
Main findings[11] Long-term IP therapy reduces HSIL recurrence in HPV-positive women who have undergone surgery.[11] Adjuvant IP immunotherapy augmented cervical HPV infection clearance and diminished cervical dysplasia relapses in patients who were positive for cervical HPV and who underwent HSIL surgery.[11]					

45, 51, 52, 56, 58, and 59 to assess the efficacy of IP treatment in 39 women with cervical HPV infection.[73] The therapeutic regimen comprised three courses of 3000 mg IP daily at 10-d intervals between courses.[73] At the end of the trial, viral load declined to a clinically insignificant level in 17.95% of all women and there was 74.36% cervical HPV clearance.[73] Over 3 y, Ordiyants et al followed 80 patients with persistent cervical HPV infection and dysplasia. They had been subjected to a combination of radio-wave conization and three courses of 1000 mg IP thrice daily for 10 d with 14 d intervals between courses.[74] At the end of the study, clearance of cervical HPV infection was confirmed for 97.5% of all patients.[74] Budanov et al assessed cervical HPV infection in 100 women aged 19–35 y.[67] Forty-four of the patients were excluded as they had mixed infections. The remaining 56 were all HPV

positive and were divided into two groups.[67] The first consisted of 25 women (44.6%) who were administered 1000 mg oral IP monotherapy thrice daily for 10 d and subjected to cervical HPV PCR after 60 d.[67] The second comprised 31 women (55.4%) with confirmed CIN1treated by electro-ablation plus 1000 mg oral IP monotherapy thrice daily for 10 d. They were subjected to cervical HPV PCR, PAP tests, and colposcopy after 60 d.[67] In the first group, clearance of cervical HPV infection was established in 17 patients (68%) and persistence in eight patients (32%). The latter were administered two additional IP courses.[67] Cervical HPV PCR revealed 88% clearance of cervical HPV infection after 6 mo.[67] In the second group, the combined treatment provided 93.5% cervical HPV clearance after 6 mo.[67] Hence, both the IP monotherapy and combined therapy had strong cervical HPV clearance efficacy.[67] Kedrova et al evaluated the efficacy of combined IP treatment in women presenting with cervical HPV16 and HPV18 infection and CIN.[75] After IP treatment, HPV16 and HPV18 were cleared in 77.8% and 50% of the women, respectively.[75] Few patients required any additional IP treatment.[75] In a subsequent study, 128 patients with cervical HPV infection and LSIL were divided into three groups and followed for up for 6 mo. In the first group, 48 women were treated for 28 d with six 0.500-mg IP tablets taken at 8-h intervals. In the second group, 41 women were treated with the same IP dose over a 14-d period. In the third group, 39 women were administered no IP.[76] After 6 mo, there was no evidence of cervical HPV infection in 93.7%,78.0%, and 43.6% of the women in the first, second, and third groups, respectively.[76] Based on the foregoing results, the authors recommended IP monotherapy for rapid clearance of cervical HPV infection.[76]

In our 6-y trial, 32 women with cervical HPV infection had undergone electroconization (loop electrosurgical excision) of the uterine cervix for established HSIL and were randomly divided into two groups. In the first group, ten patients (31.2%) were not administered postoperative IP immunotherapy while the 22 patients in the second group (68.8%) did receive it. All women were subjected to cervical tests after 24 mo and 48 mo to check for HPV persistence.[11] The patients in the second group were administered 1 g IP thrice daily at 8-h intervals for 1 mo. For the next 5 mo, the patients were administered 500 mg IP thrice daily at 8-h intervals.[11] At the end of the trial, five of the patients in the first group (15.6%) presented with cervical HPV infection whereas two of the patients in the second group (6.3%) had persistent HPV infection comprising a mixture of HPV16 and other high-risk genotypes.[11] Three patients (9.3%) from the second group had new HPV infections consisting of different genotypes.[11] At the end of the study period, only four patients (12.5%) in the second group had cervical HPV infections.[10] Two patients (6.2%) in the second group had newly established cervical HPV infections comprising various genotypes while another two patients (6.2%) in the second group had persistent HPV infections including HPV16 and other high-risk genotypes.[11] By the end of the trial, there were significant differences between groups in terms of HPV incidence. Hence, long-term IP therapy reduces HSIL recurrence in HPV-positive women who have undergone surgery.[11] Adjuvant IP immunotherapy augmented cervical HPV infection clearance and diminished cervical dysplasia relapses in patients who were positive for cervical HPV and who underwent HSIL surgery.[11]

Conclusion

- Genital intraepithelial neoplasia and corresponding cancers caused by HPV are associated with high morbidity and mortality rates. Thus, ongoing research on HPV infection, epidemiology, pathogenesis, treatment, and prophylaxis is required to reduce the incidence and severity of these diseases. There is a clear relationship between HPV and human immunity, but the underlying mechanisms have not been fully elucidated.
- The IP therapy has demonstrated good clinical efficacy in stimulating innate immunity, strengthening the host immune system, and promoting cervical HPV clearance.
- IP therapy shows promise at lowering the recurrence of cervical dysplasia and precancers caused by chronic cervical HPV infection.

Abbreviations

CCL, chemokine ligand; CXCL, C-X-C chemokine ligand; dsRNA, double-stranded ribonucleic acid; HPV, human papillomavirus; IAD, inosine acedobendimepranol; IFN, interferon; IgA, immunoglobulin A; IgC, immunoglobulin C; IL, interleukin; IMP, intramembrane plasma particle; IP, inosine pranobex; NK, natural killer; PAMP, pathogen-associated molecular pattern; ssRNA, single-stranded ribonucleic acid; TLR, Toll-like receptor; TNF, tumor necrosis factor.

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References

1. Farahmand M, Moghoofei M, Dorost A, et al. Prevalence and genotype distribution of genital human papillomavirus infection in female sex workers in the world: a systematic review and meta-analysis. *BMC Public Health*. 2020;20:1455. doi:10.1186/s12889-020-09570-z
2. Muñoz N, Castellsagué X, de González AB, Gissmann L, Castellsagué X. Chapter 1: HPV in the etiology of human cancer. *Vaccine*. 2006;24(Suppl3):1–10. doi:10.1016/j.vaccine.2006.05.115
3. Bzhalava D, Guan P, Franceschi S, Dillner J, Clifford G. A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types. *Virology*. 2013;445(1–2):224–231. doi:10.1016/j.virol.2013.07.015
4. WHO. *International Agency for Research on Cancer (IARC). IARC Monograph. Volume 100-B. Biological Agents. "Human Papillomaviruses – Epidemiology". Published by the International Agency for Research on Cancer*. Geneva 27, Switzerland: WHO Press, World Health Organization; 2012:255–313.
5. Muñoz N, Méndez F, Posso H, et al. for the Instituto Nacional de Cancerologia HPV Study Group (2004). Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis*. 2004;190:2077–2087. doi:10.1086/425907
6. Franco EL, Villa LL, Sobrinho JP, et al. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis*. 1999;180:1415–1423. doi:10.1086/315086
7. Dugué PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther*. 2013;13 (1):29–42. doi:10.1586/era.12.159
8. Conesa-Zamora P. Immune responses against virus and tumor in cervical carcinogenesis: treatment strategies for avoiding the HPV-induced immune escape. *Gynecol Oncol*. 2013;131 (2):480–488. doi:10.1016/j.ygyno.2013.08.025
9. Nguyen HH, Broker TR, Chow LT, et al. Immune responses to human papillomavirus in genital tract of women with cervical cancer. *Gynecol Oncol*. 2005;96(2):452–461. doi:10.1016/j.ygyno.2004.10.019
10. Zhou C, Tuong ZK, Frazer IH. Papillomavirus immune evasion strategies target the infected cell and the local immune system. *Front Oncol*. 2019;9:682. doi:10.3389/fonc.2019.00682
11. Kovachev S. Immunotherapy in patients with local HPV infection and high-grade squamous intraepithelial lesion following uterine cervical conization. *Immunopharmacol Immunotoxicol*. 2020;42 (4):314–318. doi:10.1080/08923973.2020.1765374
12. National Research Council. *Treating Infectious Diseases in a Microbial World: Report of Two Workshops on Novel Antimicrobial Therapeutics*. Washington, DC: The National Academies Press; 2006.
13. Maus M, Fraietta J, Levine B, Kalos M, Zhao Y, June C. Adoptive immunotherapy for cancer or viruses. *Ann Rev Immunol*. 2014;32 (1):189–225. doi:10.1146/annurev-immunol-032713-120136
14. Monjazeb A, Hsiao HH, Sckisel G, Murphy W. The role of antigen-specific and non-specific immunotherapy in the treatment of cancer. *J Immunotoxicol*. 2012;9(3):248–258. doi:10.3109/1547691X.2012.685527
15. Bascones-Martinez A, Mattila R, Gomez-Font R, Meurman JH. Immunomodulatory drugs: oral and systemic adverse effects. *Med Oral Patol Oral Cir Bucal*. 2014;19(1):e24–e31. doi:10.4317/medoral.19087
16. Ahmed RS, Newman AS, O'Daly J, et al. Inosine AcedobenDimepranol promotes an early and sustained increase in the natural killer cell component of circulating lymphocytes: a clinical trial supporting anti-viral indications. *Int Immunopharmacol*. 2017;42:108–114. doi:10.1016/j.intimp.2016.11.023
17. Sudenga SL, Shrestha S. Key considerations and current perspectives of epidemiological studies on human papillomavirus persistence, the intermediate phenotype to cervical cancer. *Int J Infect Dis*. 2013;17 (4):e216–e220. doi:10.1016/j.ijid.2012.12.027
18. Muñoz N, Hernandez-Suarez G, Méndez F, et al. Persistence of HPV infection and risk of high-grade cervical intraepithelial neoplasia in a cohort of Colombian women. *Br J Cancer*. 2009;100(7):1184–1190. doi:10.1038/sj.bjc.6604972
19. Bonde J, Bottari F, Iacobone AD, et al. Human papillomavirus same genotype persistence and risk: a systematic review. *J Low Genit Tract Dis*. 2021;25(1):27–37. doi:10.1097/LGT.0000000000000573
20. Giuliano AR, Harris R, Sedjo RL, et al. Incidence, prevalence, and clearance of type- specific human papillomavirus infections: the Young Women's Health Study. *J Infect Dis*. 2002;186:462–469. doi:10.1086/341782
21. Ho GY, Burk RD, Klein S, et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst*. 1995;87(18):1365–1371. doi:10.1093/jnci/87.18.1365
22. Venturoli S, Ambretti S, Cricca M, et al. Correlation of high-risk human papillomavirus genotypes persistence and risk of residual or recurrent cervical disease after surgical treatment. *J Med Virol*. 2008;80(8):1434–1440. doi:10.1002/jmv.21198
23. Rachel Skinner S, Wheeler CM, Romanowski B, et al. Progression of HPV infection to detectable cervical lesions or clearance in adult women: analysis of the control arm of the VIVIANE study. *Int J Cancer*. 2016;138(10):2428–2438. doi:10.1002/ijc.29971
24. Rositch AF, Koshiol J, Hudgens M, et al. Patterns of persistent genital human papillomavirus infection among women worldwide: a literature review and meta-analysis. *Int J Cancer*. 2013;133 (6):1271–1285. doi:10.1002/ijc.27828
25. Jaisamrarn U, Castellsagué X, Garland SM, et al. Natural history of progression of HPV infection to cervical lesion or clearance: analysis of the control arm of the large, randomised PATRICIA study. *PLoS One*. 2013;8(11):e79260. doi:10.1371/journal.pone.0079260
26. Miranda PM, Silva NNT, Pitol BCV, et al. Persistence or clearance of human papillomavirus infections in women in OuroPreto, Brazil. *Bio Med Res Int*. 2013;2013:578276.
27. Delvenne P. Rôle des réponsesimmunitairesdans les lésions (pré) néoplasiquescervicalesassociées aux papillomavirus humains [Immunologic response to (pre)neoplastic cervical lesions associated with human papillomavirus]. *Bull Mem Acad R Med Belg*. 2005;160 (5–6):287–293. French.
28. Amador-Molina A, Hernández-Valencia JF, Lamoyi E, Contreras-Paredes A, Lizano M. Role of innate immunity against human papillomavirus (HPV) infections and effect of adjuvants in promoting specific immune response. *Viruses*. 2013;5(11):2624–2642. doi:10.3390/v5112624
29. Stanley MA, Sterling JC. Host responses to infection with human papillomavirus. *Curr Probl Dermatol*. 2014;45:58–74.
30. Smola S. Immunopathogenesis of HPV-associated cancers and prospects for immunotherapy. *Viruses*. 2017;9(9):254. doi:10.3390/v9090254
31. Barros MR, de Melo CML, Barros ML, de Cássia Pereira de Lima R, de Freitas AC, Venuti A. Activities of stromal and immune cells in HPV-related cancers. *J Exp Clin Cancer Res*. 2018;37(1):137. doi:10.1186/s13046-018-0802-7

32. Sheu BC, Chang WC, Lin HH, Chow SN, Huang SC. Immune concept of human papillomaviruses and related antigens in local cancer milieu of human cervical neoplasia. *J Obstet Gynaecol Res*. 2007;33(2):103–113. doi:10.1111/j.1447-0756.2007.00492.x
33. Woodby B, Scott M, Bodily J. The interaction between human papillomaviruses and the stromal microenvironment. *Prog Mol Biol Transl Sci*. 2016;144:169–238.
34. Deligeoroglou E, Giannouli A, Athanasopoulos N, et al. HPV infection: immunological aspects and their utility in future therapy. *Infect Dis Obstet Gynecol*. 2013;2013:540850. doi:10.1155/2013/540850
35. Lee SJ, Yang A, Wu TC, Hung CF. Immunotherapy for human papillomavirus-associated disease and cervical cancer: review of clinical and translational research. *J Gynecol Oncol*. 2016;27(5):e51. doi:10.3802/jgo.2016.27.e51
36. Barros MR, de Oliveira THA, de Melo CML, Venuti A, de Freitas AC. Viral modulation of TLRs and cytokines and the related immunotherapies for HPV-associated cancers. *J Immunol Res*. 2018;2018:2912671. doi:10.1155/2018/2912671
37. Singh M, Thakral D, Rishi N, Kar HK, Mitra DK. Functional characterization of CD4 and CD8 T cell responses among human papillomavirus infected patients with anogenital warts. *Virus Dis*. 2017;28(2):133–140. doi:10.1007/s13337-017-0382-8
38. Nasu K, Narahara H. Pattern recognition via the toll-like receptor system in the human female genital tract. *Mediat Inflamm*. 2010;2010:976024. doi:10.1155/2010/976024
39. Yang K, Puel A, Zhang S, et al. Human TLR-7-, −8-, and −9-mediated induction of IFN-alpha/beta and -lambda Is IRAK-4 dependent and redundant for protective immunity to viruses. *Immunity*. 2005;23:465–478. doi:10.1016/j.immuni.2005.09.016
40. Miller LS, Modlin RL. Human keratinocyte Toll-like receptors promote distinct immune responses. *J Investig Dermatol*. 2007;127:262–263. doi:10.1038/sj.jid.5700559
41. Sasagawa T, Takagi H, Makinoda S. Immune responses against human papillomavirus (HPV) infection and evasion of host defense in cervical cancer. *J Infect Chemother*. 2012;18(6):807–815. doi:10.1007/s10156-012-0485-5
42. Sparber F. Langerhans cells: an update. *J Germ Soc Dermatol*. 2014;12(12):1107–1111.
43. Woo YL, van den Hende M, Sterling JC, et al. A prospective study on the natural course of lowgrade squamous intraepithelial lesions and the presence of HPV16 E2-, E6- and E7-specific T-cell responses. *Int J Cancer*. 2010;126(1):133–141. doi:10.1002/ijc.24804
44. Vici P, Pizzuti L, Mariani L, et al. Targeting immune response with therapeutic vaccines in premalignant lesions and cervical cancer: hope or reality from clinical studies. *Expert Rev Vaccines*. 2016;15(10):1327–1336. doi:10.1080/14760584.2016.1176533
45. You Y, Wang L, Li Y, et al. Multicenter randomized study of inosine pranobex versus acyclovir in the treatment of recurrent herpes labialis and recurrent herpes genitalis in Chinese patients. *J Dermatol*. 2015;42(6):596–601. doi:10.1111/1346-8138.12845
46. Brzeski M, Madhok R, Hunter JA, Capel HA. Randomised, double blind, placebo controlled trial of inosine pranobex in rheumatoid arthritis. *Ann Rheum Dis*. 1990;49:293–295. doi:10.1136/ard.49.5.293
47. Sliva J, Pantzartzi CN, Votava M. Inosine pranobex: a key player in the game against a wide range of viral infections and non-infectious diseases. *Adv Ther*. 2019;36(8):1878–1905. doi:10.1007/s12325-019-00995-6
48. Petrova M, Jelev D, Ivanova A, Krastev Z. Isoprinosine affects serum cytokine levels in healthy adults. *J Interferon Cytokine Res*. 2010;30(4):223–228. doi:10.1089/jir.2009.0057
49. Lasek W, Janyst M, Wolny R, Zapala L, Bocian K, Drela N. Immunomodulatory effects of inosine pranobex on cytokine production by human lymphocytes. *Acta Pharm*. 2015;65(2):171–180. doi:10.1515/acph-2015-0015
50. Milano S, Dieli M, Millott S, Miceli MD, Maltese E, Cillari E. Effect of isoprinosine on IL-2, IFN-gamma and IL-4 production in vivo and in vitro. *Int J Immunopharmacol*. 1991;13(7):1013–1018. doi:10.1016/0192-0561(91)90055-C
51. Tsang KY, Pan JF, Swanger DL, Fudenberg HH. In vitro restoration of immune responses in aging humans by isoprinosine. *Int J Immunopharmacol*. 1985;7(2):199–206. doi:10.1016/0192-0561(85)90027-X
52. Sabat R, Grutz G, Warszawska K, et al. Biology of interleukin-10. *Cytokine Growth Factor Rev*. 2010;21(5):331–344. doi:10.1016/j.cytogfr.2010.09.002
53. Ohnishi H, Kosuzume H, Inaba H, Ohkura M, Shimada S, Suzuki Y. The immunomodulatory action of inosiplex in relation to its effects in experimental viral infections. *Int J Immunopharmacol*. 1983;5(3):181–196. doi:10.1016/0192-0561(83)90055-3
54. Isoprinosine. Summary of product characteristics. Ewopharma International; 2003. Available from: http://www.doctoronline.bg. Accessed May 28, 2021.
55. Renoux G, Renoux M, Guillaumin J-M. Isoprinosine as an immunopotentiator. *J Immunopharmacol*. 1979;1(3):337–356. doi:10.3109/08923977909026379
56. Krastev Z, Jelev D, Ivanova R. Isoprinosine induces a rapid lympho-mononuclear response in adult participants. *Med Inf*. 2015;2(1):80–85.
57. Corey L, Chiang W, Reeves W, Stamm W, Brewer L, Holmes K. Effect of isoprinosine on the cellular immune response in initial genital herpes virus infection. *Clin Res*. 1979;27:41A.
58. Galbraith GM, Thiers BH, Fudenberg HH. An openlabel trial of immunomodulation therapy with inosiplex (Isoprinosine) in patients with alopecia totalis and cell-mediated immunodeficiency. *J Am Acad Dermatol*. 1984;11(2):224–230. doi:10.1016/S0190-9622(84)70153-8
59. Cianciara J, Laskus T, Gabinska E, Loch T. Isoprinosine in the treatment of chronic active hepatitis type B. *Scand J Infect Dis*. 1990;22(6):645–648. doi:10.3109/00365549009027115
60. Diaz-Mitoma F, Turgonyi E, Kumar A, Lim W, Larocque L, Hyde BM. Clinical improvement in chronic fatigue syndrome is associated with enhanced natural killer cell-mediated cytotoxicity: the results of a pilot study with isoprinosine. *J Chronic Fatigue Syndr*. 2003;11(2):71–95. doi:10.1300/J092v11n02_06
61. Sadoul G, Beuret TH. Treatment of cervical and vulvar condylomata by CO_2 laser also with a immunostimulant. *Rev Fran Gynecol Obstet*. 1984;79(11):681–684.
62. Mohanty KC, Scott CS. Immunotherapy of genital warts with inosine pranobex (Imunovir): preliminary study. *Sex Transmit Infect*. 1986;62:352–355. doi:10.1136/sti.62.5.352
63. Davidson-Parker J, Dinsmore W, Khan MH, Hicks DA, Morris CA, Morris DF. Immunotherapy of genital warts with inosine pranobex and conventional treatment: double blind placebo controlled study. *Genitourin Med*. 1988;64(6):383–386. doi:10.1136/sti.64.6.383
64. Nejmark BA, Kondrateva JS, Zologina VS, Torbik DV. Effectiveness of combined treatment of HPV infection. *Urologia*. 2015;(2):39–40,42.
65. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS*. 1996;7(4):276–280. doi:10.1258/0956462961917960
66. Rakhmatulina MR. Combination therapy for papillomavirus infection. *Akusherstvoi Ginekologiya/Obstet Gynecol*. 2017;12:122–125. Russian.
67. Budanov PV, Churganova AA, Bakhtiyarov KR, Strizhakov AN. Human papillomavirus infection: the efficacy of treatment with inosine pranobex. *Gynecology*. 2015;17(6):56–59. doi:10.26442/2079-5696_17.6.56-59
68. Bitsadze VO, Khamani NM, Makatsariya NA. Role of inosine pranobex in management of HPV-associated diseases: problems and prospective. *Obstet Gynecol Reprod*. 2016;10(3):76–84. Russian. doi:10.17749/2313-7347.2016.10.2.076-084

69. Prilepskaya VN, Rogovskaya SI. Possibilities of isoprinosine in treatment of chronic cervicitis and vaginitis. *Russ Med J*. 2008;16(1):5–9.
70. Linask LI, Grigorieva EE. Experience of the use of Isoprinosin against cervical diseases in the adolescents and young women with papillomavirus infection. *Russ Med J*. 2008;16(19):1221–1225.
71. Eliseeva MY, Manukhin IB, Mynbaev OA, Zvereva NS, Mishutina AA, Tcarev VN. Antiviral effect of isoprinosine in HPV-associated diseases. *Obstet Gynecol*. 2012;2:107–114.
72. Pestrikova TY, Pushkar VA. Evaluation of comprehensive treatment of cervical pathology associated with HPV. *Gynecol*. 2015;17 (1):50–53. doi:10.26442/2079-5831_17.4.50-53
73. Pestrikova TY, Panfilova YO, Yurasova EA, Kotelnikova AV. Assessment of viral load in patients with HPV-associated cervicitis during the course of complex treatment. *Gynecology*. 2017;19 (3):45–48.
74. Ordiyants IM, Buyanova NV, Abdurakhmanova MB. Recurrence of HPV infection after combination therapy of uterine cervical diseases. *Obstet Gynecol News Opin Train*. 2018;6(3):47–52.
75. Kedrova AG, Podisov YI, Kuznetsov VV, Bryugzin VV, Kozachenko VP, Nikogosyan SO. Role of antiviral therapy in the complex treatment of patients with epithelial dysplasias and preinvasive cancer of the cervix uteri. *Akush Ginekol*. 2006;6:27–30.
76. Kedrova AG. Local immunosuppressive damage in the human papillomavirus persistence. *RMJ*. 2017;26:1971–1976.