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REVIEW ARTICLE

The impact of systemic psoriasis treatments on human papillomavirus activation and propagation

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Abstract

Psoriasis is one of the most prevalent diseases in the world and it affects up to 2% of the worldwide population. Its pathogenesis is complex and the lesions may be triggered by multiple factors. Human papillomavirus (HPV) is associated with anogenital cancers, cutaneous warts and is considered one of the most prevalent infections in the world. In this review, the available literature on the systemic treatment of patients with psoriasis and concomitant HPV infection was analysed.

KEYWORDS

HPV, human papillomavirus, psoriasis, treatment methods

INTRODUCTION

Psoriasis is a common, chronic inflammatory skin disease that affects up to 2% of the worldwide population.[1] Its pathogenesis is complex and consists of immunological and genetic factors, including the skin microbiome. It may also be triggered by various environmental circumstances, such as injury, smoking, stress, etc. At the cellular level, its main issue is an inflammation that leads to uncontrolled keratinocyte proliferation and differentiation.[2]

Human papillomavirus (HPV) is associated with one of the most prevalent infections in the world. Not only it is the main cause of cervical cancer (mostly HPV 16, HPV 18), but it may also evoke anogenital (HPV 6 and HPV 11) and cutaneous warts (most commonly HPV 2, 4, followed by types 1, 3, 27, 29, 57)[3] – usually set on the acral, palmar or dorsal locations. Moreover, it also takes part in the pathogenesis of some of the aerodigestive tract cancers. It is widely discussed that sexually active men and women are most likely to be infected with HPV at least once in their lifetime, without developing any symptoms.[4]

There are a number of studies evaluating the association of HPV incidence with the onset of psoriasis. A case report published in 2015 assumed that a condyloma acuminata might have caused a breakout of psoriasis lesions in a 20-year-old patient.[5] A recent, twelve-year population study by Chen et al.[6] based on over sixty-six thousand patients, showed an association between an HPV infection and an increased risk of developing psoriasis. Mahe et al.[7] and Favre et al.[8] described a higher prevalence of the Epidermodysplasia Verruciformis (EV) HPV genotype, especially HPV 5 and HPV 36 in patients with psoriasis than in the general population. Mahe et al.[7] suggested that these viruses may contribute to the pathogenesis of psoriasis. Cronin et al.,[9] however, implied that the psoriatic skin may be more permissive for the presence of HPV than normal skin but not specifically for HPV 5 or HPV 36.

The Psoriasis Area Severity Index (PASI) above 10 (moderate psoriasis to severe psoriasis) may indicate the need to use phototherapy or add systemic medications to improve the patient's quality of life and skin condition. Moreover, lesions located in some special regions, such as the scalp, hands and feet, nails and intertriginous areas may also require systemic treatment regardless of the PASI score. In predisposed patients, applied treatment may have a relevant impact on HPV activation and propagation.

Topical drugs are often used in the mild symptoms of psoriasis (PASI < 10) or simultaneously in the treatment of patients who require systemic therapy. They may also have a significant impact on the course of diseases caused by HPV on the skin. The most commonly used topical steroids applied especially to areas typical for HPV infections,

such as the anogenital region, can reactivate HPV.[10] Wider considerations on the subject of local therapy were not the topic of research in this publication; however, the authors are aware that this issue would be worth discussing to a greater extent in a separate article.

METHODS

The review of the literature was performed by searching the PubMed database in June 2021. The authors used the following search terms: 'psoriasis' [MesH term] or 'acitretin' [MesH term], or 'methotrexate' [MesH term], or 'cyclosporine' [MesH term], or 'dimethyl fumarate' [MesH term], or 'biological drugs', or 'biological products' [MesH term], or 'infliximab' [MesH term], or 'etanercept' [MesH term], or 'adalimumab' [MesH term], or 'certolizumab', or 'ustekinumab' [MesH term], or 'guselkumab', or 'risankizumab', or 'tildrakizumab', or 'secukinumab', or 'ixekizumab', or 'brodalumab', or 'apremilast', or 'phototherapy' [MesH term], or 'photochemotherapy' [MesH term], or 'PUVA' and 'hpv', or 'human papillomavirus', or 'hpv infection', or 'alpha-papillomavirus' [MesH term], or 'papillomavirus infections' [MesH term]. The initial search revealed 405 results. After applying additional criteria (English language publications), the database search revealed 380 records. After an initial screening of the titles, we selected 118 articles. After a full-text article assessment and adding a few articles from references, we chose the most representative studies, eventually obtaining 23 results. Each study was assigned a level of evidence according to the 2011 Oxford Centre for Evidence-Based Medicine levels of evidence guidelines. The treatment modalities were divided based on drug types and the available data was assessed.

RESULTS

Among the 23 analysed articles, the majority were case reports (12), followed by cohort studies (3), systematic reviews and meta-analysis (2), a randomized, controlled study (1), comparative study (1), prospective pilot study (1), prospective controlled observation study with a cross-sectional analysis (1), expert consensus (1), case series (1). A total of 1315 cases were described. Reports concerned the treatment of patients with the use of phototherapy, acitretin/ retinoids, methotrexate, cyclosporine, TNF-alpha inhibitors (infliximab, etanercept), IL12/23 inhibitor (ustekinumab), IL-17 inhibitor (secukinumab). Most of the reports concerned the treatment of patients with Acitretin/Retinoids (541 patients). Then treatment with methotrexate (352), TNF-alpha inhibitors (228 patients), phototherapy (152), IL17 inhibitor – secukinumab (37), IL12/23 inhibitor – ustekinumab (3), cyclosporine (2). There was no data regarding dimethyl fumarate, apremilast and other biological drugs, such as IL23 inhibitors, other TNF-alpha inhibitors and other IL17 inhibitors.

A summary of the analysed articles and the results obtained by the authors is presented in Table 1.

Phototherapy

UV radiation and HPV might affect cell-repair mechanisms. UV radiation induces mutations in the p53 and causes local and systemic immunosuppression.[11] In the 90's it was discovered that 2 HPV high-risk oncoproteins (E6 and E7) interact with 2 important proteins (p53 and Rb), thus they can interfere with cell apoptosis.[11,12] Low-risk HPV, which is much more common in skin lesions, can also bind p53 and Rb, but with lower affinity and without interfering with cell cycle control.[13]

Wolf et al.'s[13] cohort study on 81 patients analysed the presence of HPV sequences in DNA isolated from plucked body hairs from non-diseased skin on the arms, legs and trunk of patients with psoriasis with a history of PUVA exposure. The rate of HPV-DNA positivity was significantly higher in a group of patients with a history of PUVA exposure (73% patients with skin cancer and 69% with no skin cancer history), compared to 36% patients with no history of PUVA exposure or skin cancer. The authors concluded that the prevalence of HPV in the non-lesional skin (hair follicles) of patients with psoriasis who have a history of PUVA exposure is increased.

In a comparative study on 70 patients (60 with psoriasis and 10 healthy volunteers), Salem et al.[14] studied the presence of HPV in untreated (20) and ultraviolet-treated skin (20 with PUVA, 20 with NB-UVB). They examined for HPV expression using skin tissue biopsy from lesional non-sun-exposed skin (to avoid the effect of natural UV exposure) and a nested polymerase chain reaction (PCR). HPV expression in patients with psoriasis on PUVA treatment was significantly higher (60%) compared with NB-UVB-treated psoriasis (20%), untreated psoriasis (0%) and normal control group (20%). There was no significant difference in the incidence of HPV in the group treated with NB-UVB compared to the untreated psoriasis or control group. Considering the above, PUVA therapy appears to have a greater effect on the development of HPV infection. When deciding on phototherapy as a method of treatment in psoriasis patients with a history of HPV one should lean towards NB-UVB.

Rust et al.[15] described in a case report an 81-year-old immunocompetent woman with a history of psoriasis and extensive ultraviolet radiation (UVR) exposure

TABLE 1 Therapeutic options for moderate/severe psoriasis in patients with Human papillomavirus (HPV) infections based on the available literature

Treatment options	Study type		Patients	Level of evidence	Outcome	Reference
Phototherapy	PUVA/NB-UVB	Comparative study	70	III	The prevalence of HPV-DNA is increased in PUVA-treated skin and not increased in NB-UVB-treated skin compared with untreated psoriasis and control group	Salem et al.[14]
	PUVA	Cohort Study	81	III	The prevalence of HPV-DNA in the PUVA-treated patients with psoriasis is increased compared to untreated patients	Wolf et al.[13]
	Natural UVR	Case report	1	V	Multiple HPV-positive SCC in UV-exposed skin in a psoriatic patient	Rust et al.[15]
Retinoids	Systematic review and meta-analysis		141	I	Retinoids are an effective and safe treatment for genital warts	Oren Shabatai et al.[17]
	Systematic review and meta-analysis		399	I	Retinoids are effective in the treatment of cutaneous warts	Oren Shabatai et al.[19]
	Expert consensus		-	V	First-line recommended drug in patients with psoriasis and HPV infection	Strober et al.[20]
	Case report		1	V	Successful treatment of giant condyloma acuminatum with acitretin combined with Interferon-γ)	Tian et al.[16]
Methotrexate (MTX)	Cohort cross-section study		33	III	Does not significantly increase the rate of lower genital tract HPV infections in patients with juvenile arthritis	Ferreira et al.[22]
	Retrospective cohort study		257	III	No increased risk of cervical carcinoma or CIN in female patients with atopic dermatitis	Garritsen et al.[23]
	A randomized, controlled study		60	II	Poor efficacy of intralesional MTX in the treatment of plantar warts	[24] Abdo et al.
	Case report		2	V	The potential role as a cocarcinogen promoting SCC development in patients with psoriasis	Zumtobel et al.[25]
Cyclosporine	Case report		1	V	Buschke-Löwenstein-type giant penile condyloma triggered during cyclosporine therapy for psoriasis	Piepkorn et al.[26]
	Case report		1	V	Extensive genital warts triggered after cyclosporine for psoriasis	[27] Campoli et al.
	Expert consensus		-	V	The least recommended treatment in psoriasis and concomitant HPV infection	Strober et al.[20]
Dimethyl Fumarate	No data available					
Apremilast	No data available					
TNF-alpha inhibitors	Prospective controlled observation study with a cross-sectional analysis		222	II	TNF-alpha blockade does not increase the prevalence of anogenital HPV infection or disease in psoriasis and inflammatory bowel diseases	Handisurya et al.[35]
	Case report		2	V	Exacerbation of HPV after etanercept and infliximab for psoriasis	Antoniou et al.[32]
	Case report		3	V	Exacerbation of HPV after using infliximab for psoriasis	Georgala et al.[33]
	Case report		1	V	Exacerbation of HPV lesions in patient with Crohn's disease after infliximab	Somasekar et al.[34]

(Continues)

TABLE 1 (Continued)

Treatment options	Study type	Patients	Level of evidence	Outcome	Reference
Ustekinumab	Case report	1	V	Appearance of disseminated verrucous lesions after 6 months of psoriasis therapy	Anderson et al.[36]
	Case report	1	V	Appearance of a bulky condyloma acuminata shortly after starting treatment for psoriasis	Burlando et al.[37]
	Case report	1	V	Development of viral warts after 2 months of therapy for Crohn's disease	Svoboda et al.[38]
Secukinumab	Prospective pilot study	32	IV	Decrease in detection of HPV-DNA in eyebrows and skin scrapings during psoriasis therapy	Chiu et al.[39]
	Case series	4	V	Successful treatment of digital and plantar chronic warts during psoriasis therapy. Decrease in the number of detected HPV types	Brunet-Possenti et al.[40]
	Case report	1	V	Successful treatment of an active HPV infection during psoriasis therapy	Ayhan et al.[41]

The Oxford 2011 Levels of Evidence were used to classify the level of evidence of each article; the levels of evidence: I – a systematic review and meta-analysis of randomized controlled trials (RCT or high quality RCT); II – lesser quality randomized control trials or prospective comparative studies; III – case control studies or retrospective studies; IV –case series without the use of comparison or control groups; V – case reports or expert opinion.

during adulthood (with no history of medically administered UV therapy for psoriasis) who experiences multiple HPV-positive SCC. In their study, they used PCR to examine for HPV expression in SCCs (9 specimens from a sun-exposed skin of a lower extremity) and normal skin (3 specimens from a right arm, left leg and right back). Only one specimen from normal skin (right back) was derived from non-sun-exposed skin. None of the specimens were from lesional psoriatic skin. HPV DNA was detected in 5 out of 9 SCCs and in only one specimen of normal skin (left leg, sun-exposed skin). The authors concluded that this case report suggests an association between psoriasis, an HPV infection and UVR exposure, in the onset of SCC. HPV DNA is often detected in patients with psoriasis who are often treated with phototherapy. UVR is the major known risk factor in the occurrence of non-melanoma skin cancer (NMSC). What is more, HPV can be a possible cofactor in the onset of SCC. UVR and HPV may cooperate to initiate or induce the progression of SCC. It is important to remember this potential connection when choosing the right therapy for patients with psoriasis, especially for elderly people who have impaired DNA repair mechanisms. It should be noted that a full body examination should always be done (with an adjunctive role of dermoscopy if needed) before starting phototherapy, to detect skin lesions suspicious for malignancy.

Retinoids

Retinoids are considered to have good efficacy and safety in the treatment of genital warts in trials and systematic meta-analyses. They have been used for their antiproliferative, proapoptotic and antioxidant features, and they might also have an immunomodulatory, inhibitory effect on HPV replication.[16,17] Regardless, according to William Helm et al.'s Cochrane review, they do not seem to prevent progression of cervical intraepithelial neoplasia (CIN) of any grade.[18]

A systematic review and meta-analysis by Oren-Shabtai et al., encompassing 141 patients with genital warts, who were treated only with retinoids, compared the efficacy of tretinoin 0.05% cream, oral isotretinoin and oral etretinate.[17] Both topical and systemic retinoids were effective in the treatment of genital warts and were associated with a 51% clearance rate. Isotretinoin was the most examined drug in 127 patients (90% of the featured group) with a 56% clearance rate. Oral etretinate had the best results (60% clearance rate), but only 3 patients were included in the study, which may not be enough to set sufficient conclusions. The topical tretinoin was the least effective among the tested drugs, and its partial response was at

36%. The analysis did not feature acitretin, which is the most common retinoid used in the systemic treatment of psoriasis.

Another review and meta-analysis by Oren-Shabatai et al. featured 399 patients who were treated with retinoids for cutaneous warts.[19] Similarly to the previously discussed study, this one also showed that both systemic and topical retinoids were effective in the treatment of cutaneous warts, with a complete response rate of 61% and 64%, respectively. Among topical retinoids, adapalene gave the highest complete response, and vitamin A 2% ointment was the lowest. In the group of systemic retinoids, etretinate (75%) showed the best results, then isotretinoin (71%) and acitretin (39%). However, etretinate was only evaluated in one prospective cohort study (12% of the patients featured in the review) while 46% and 42% of patients were on isotretinoin and acitretin, respectively.

An expert consensus published in 2012 (Delphi Consensus Approach to Challenging Case Scenarios in Moderate-to-Severe Psoriasis),[20] in which 14 experts in the field of psoriasis discussed the most challenging treatment problems using the Delphi process, ranked NB-UVB and phototherapy with acitretin as the most reasonable treatment options for psoriatic patients with an active HPV-induced cervical and anogenital dysplasia.

Acitretin has also been described as a part of an efficient treatment option in combination with interferon gamma in a case report describing a 16-year-old patient with a giant condyloma acuminatum.[16]

The data above demonstrates the safety of retinoids in patients with psoriasis and HPV-associated lesions, proving them to be good systemic solutions, especially for men and post-pubertal women. The main retinoid used in psoriasis, acitretin has its limitations – it should not be used in women of childbearing age because of its teratogenic effect. Meanwhile, HPV infections peak in women between 20 and 29 years of age.[21] While oral isotretinoin might not be as effective in psoriasis treatment, it might be considered in some cases for reproductive-age females due to the fact that it does not require as long a contraceptive period as in the case of acitretin therapy.

Methotrexate

Methotrexate (MTX) is largely used in dermatology and rheumatology, and it is known for its anti-proliferative, anti-inflammatory and immunomodulating features. Its influence on psoriatic patients with an HPV infection is unclear. There is contrasting information in the available literature suggesting that MTX does not affect the course of an HPV-induced disease or may potentially exacerbate it.

A cross-section study by Ferreira et al. on lower genital tract infections in 33 patients with juvenile arthritis on 15–20 mg of methotrexate per week tested cervical specimens for the presence of HPV, Chlamydia trachomatis and Neisseria gonorrhoeae DNA.[22] The frequency of HPV infection was higher in juvenile arthritis patients than in controls, however, without statistical significance (30% vs. 11%, $p = 0.155$); therefore, the authors assumed that the drug does not seem to increase the risk of HPV infections. Identified HPV infections were mild, subclinical and significantly associated with cervical abnormalities with no clue of cervical cancer.

In Garritsen et al.'s[23] retrospective cohort study on atopic dermatitis, female patients treated with immunosuppressive agents for more than 2 months were investigated for the occurrence of cervical carcinoma and CIN. The study included 257 females, of which 9 patients were on MTX therapy and 104 patients on more than one treatment method – CsA, MTX, mycophenolate mofetil, azathioprine. No cervical carcinoma was reported in the study group; 4 patients were diagnosed with different stages of CIN (CIN II-CIN III) but none of them were taking methotrexate as monotherapy. The authors pointed out that the incidences of clinically relevant CIN II and CIN III lesions seem to be no different from the literature data of the general population.

A randomized, controlled study on 60 patients by Abdo et al.[24] analysed the effect of intralesional methotrexate on viral warts. The study group was injected with 2 mg/ml MTX intralesionally once a week for a maximum of 6 weeks. Within this group, 2 patients (6.7%) showed improvement, 8 (26.7%) showed partial improvement, and 20 (66.7%) patients showed no results. But there was no statistically significant difference between the therapeutic responses to intralesional MTX injections in patients with viral warts compared to saline injections used in the control group. The authors concluded that MTX showed poor efficacy in the treatment of plantar warts.[23]

Zumtobel et al.[25] described two patients with a long history of psoriasis treated with PUVA followed by MTX who developed activated skin cancers – the first patient developed 33 biopsy-documented, while the second 24 in situ and invasive SCCs. Moreover, in these cases, oncogenic HPV-5, HPV-14 and HPV-20 types were detected by PCR in both skin tumours and psoriatic lesions. There was no positive history for arsenic therapy or ionizing radiation. Both patients had undergone long (over 10 years) PUVA therapy before starting methotrexate and in both presented cases the first SCC occurred 1 year after initiating MTX therapy. The authors highlighted the potential role of MTX as a cocarcinogen promoting SCC development in patients with a history of long-term PUVA therapy, regarding the chronology of SCC progression soon

after MTX introduction in the presented cases and also previous literature reports. This seems to be particularly important given the frequent clinical situations in which many patients have undergone phototherapy, including PUVA, before incorporating another therapeutic option like MTX, especially when an HPV infection is additionally diagnosed at some stage.

Cyclosporine

The data on cyclosporine's effect on psoriatic patients can be found in case reports which describe genital warts and HPV-related carcinomas linked to the use of cyclosporine in psoriatic patients.

A case report from 1993 described an appearance of penile carcinoma in a 25-year-old man after a 4-year use of cyclosporine for pustular psoriasis.[26] Another case described an 18-year-old female patient who was prescribed cyclosporine due to an aggravation of psoriatic lesions.[27] The patient was previously treated successfully with TNF-alpha inhibitors, then she was put on phototherapy and topical therapy with an insufficient outcome. She developed condyloma acuminata after 3 months of treatment with cyclosporine with PCR showing HPV-11 positive results (notably, the patient underwent an HPV-16 and 18 vaccination prior to the treatment). Two months after stopping cyclosporine, the lesions spontaneously regressed.

The aforementioned Delphi Consensus[20] listed cyclosporine as the least recommended drug in the treatment of psoriatic patients with concomitant HPV infection.

It is also known that cyclosporine, as a part of the immunosuppressant treatment in transplant recipients, increases the risk of HPV replication due to the inhibition of cell-mediated immunity that is responsible for managing HPV infections.[27,28] However, it is worth remembering that the risk of developing HPV-induced cancers increases parallel to the duration of immunosuppressive treatment, which is usually set for a lifetime in patients after kidney transplantations. Furthermore, transplant receivers are usually put on multiple medications, enhancing the immunosuppression and a chance for a malignant transformation or a viral infection.

Dimethyl Fumarate

Its mechanism in the treatment of psoriasis has not been truly discovered; it is suspected that its immunomodulatory effect reduces inflammation and inhibits keratinocyte proliferation. A European Consensus on the clinical use of Dimethyl fumarate (DMF) in psoriatic patients says that screening for some viral infections such as hepatitis B/C, latent tuberculosis, or HIV is not recommended.[29] However, it does not mention anything about HPV infections.

Apremilast

Apremilast is a small molecule inhibitor of phosphodiesterase 4. It does not affect any cytokine but restores balance in the pro-inflammatory and anti-inflammatory response.[30] A cohort study on over ten thousand patients exposed to apremilast (alone or in combination with other biologics) showed no higher risk of new or recurrent infections of herpes zoster, tuberculosis and hepatitis C.[31] There was no increased risk of other infections in the studies published so far.[30] Nevertheless, there have been no trials comparing its effect on patients with HPV infection, so it's difficult to assess whether this drug can be used in patients with both of the discussed diseases, thus more studies are needed.

Biological drugs

They can increase the risk of acquisition and reactivation of bacterial, viral, or fungal infections. There are several case reports describing new appearance or exacerbation of HPV or molluscum contagiosum (MSC) lesions during treatment with TNF-alpha inhibitors. Antoniou et al.[32] reported 1 case of a 31-year-old woman with psoriasis and psoriatic arthritis who had a recurrence of genital human papillomavirus (HPV) after treatment with etanercept and 1 case of a 29-year-old patient with chronic plaque psoriasis who had HPV exacerbation and occurrence of molluscum contagiosum after infliximab infusion. Georgala et al.[33] reported a case series of three patients with psoriasis on infliximab who developed HPV/MC lesions within a few months after the initiation of infliximab infusions. Somasekar et al.[34] described a case report of a 23-year-old man with Crohn's disease who developed profuse genital warts after two doses of infliximab. These cases were treated successfully with standard cryotherapy and no relapse of wart formation was observed after discontinuation of anti-TNF-α treatment.

However, a prospective, open, controlled observation study with a cross-sectional analysis on 222 patients with psoriasis (113) or inflammatory bowel disease (IBD) (109) by Handisurya et al.[35] did not show an increased risk of anogenital HPV infection or disease appearing in TNF-alpha inhibitors therapy within 30 months of therapy. The authors of this study performed mucosal swabs for high- and low-risk HPV-DNA, serological tests (HPV6, 16 and 18) in all patients and cervical smear cytology in the

female group (88). The results were compared between the designated four groups: TNF-alpha monotherapy, monotherapy with purine analogues or folic acid, combination therapy of the two previous methods, and a group with alternative therapy or no therapy. Anogenital warts were observed in 2.7% of participants but were not associated with anti-TNF-alpha therapy. There were no statistically significant differences between the groups when analysing the frequency of HPV-DNA positivity in mucosal swabs and cervical cytology results.

The available data on these drugs are inconclusive. However, taking under consideration the level of evidence in the available publications, TNF-alpha inhibitors appear to be a relatively safe group of drugs in the discussed issue, but caution and detailed clinical evaluation of the patient during treatment is advisable.

Ustekinumab (IL12/23 antagonist) is another drug used in the treatment of moderate-to-severe psoriasis with a different mechanism of action. Anderson et al.[36] described the case of a 54-year-old man with psoriasis and psoriatic arthritis who developed disseminated verrucae after 6 months of therapy with ustekinumab. Burlando et al.[37] described a case of a 31-year-old man with psoriasis who developed de novo bulky condyloma acuminata after 3 months of treatment with ustekinumab. Svoboda et al.[38] described the case of a 59-year-old patient who developed warts after 2 months of ustekinumab therapy for Crohn's disease. The suspected mechanism of this would be the fact that blockage of the IL12/IL23 causes the decrease in the Th1 response, lowering of the IL-2 and IFN-1 levels and – due to that – weakening of the patient's ability to overcome the HPV infection.[36,38] Nonetheless, there are new IL23 antagonists (guselkumab, risankizumab, tildrakizumab) with no data on whether they may have a similar effect on HPV infected patients. Given the number and strength of available data on ustekinumab, it is difficult to draw firm conclusions.

IL-17 plays an important role in the pathogenesis of psoriasis and has become a target for another group of biological drugs. HPV increases the secretion of IL-17, which induces the proliferation of keratinocytes. In an observational and prospective pilot study on 32 patients Chiu et al.[39] observed a significant decrease in detection of HPV-DNA in eyebrow hairs, and skin scrapings during the therapy with secukinumab (anti-IL-17 agent) comparing results from the baseline (43.8%, 56.3%, respectively), after 24 (32.3%, 51.6%) and 156 weeks (20.6%, 20.6%) of treatment. In a case series of 4 patients treated with secukinumab Brunet-Possenti et al.[40] described successful treatment of digital or plantar chronic warts and a marked decrease in the number of HPV types. There is also a case report of a 37-year-old male patient with psoriasis and warts, in whom both lesions disappeared after 5 months of secukinumab treatment.[41] The IL-17 inhibition pathway may be the key to the successful treatments of both psoriasis and HPV infections. This group of drugs appears to be a promising and safe therapeutic option in psoriasis patients with concomitant HPV infection. Further studies on a larger group of patients are needed.

Human papillomavirus vaccination

Vaccination against HPV is also worth considering. Vaccination against HPV is recommended in the United States for unvaccinated males and females up to the age of 26, before or during immunosuppressive treatment.[42] Vaccines against HPV provide considerable protection of immunocompetent individuals, especially against the HPV types that may cause genital neoplasms and cutaneous warts.[29,42] It is not known whether patients receiving anti-TNF-alpha therapy have an altered response to the HPV vaccination. Early vaccination increases the range of possible treatment options in case of a psoriasis flare-up that may require systemic treatment.

Human papillomavirus screening

In principle, HPV screening only affects women and is directly related to the prevention of cervical cancer. Recommendations vary by region of the world, nevertheless, screening programs should always be widely promoted. For example, the International Union against Sexually Transmitted Infections (IUSTI) recommendations for the management of anogenital warts advise that female patients should be informed about cervical cytology screening as per local or national guidelines.[43]

American Societies recommend that in females younger than 21 years old no screening is needed. Women aged 21–29 should have cytology done without HPV testing. Females aged 30–65 should have cytology alone every 3 years or cytology with HPV testing every 5 years. Women older than 65 years require no testing after prior negative screening results (two consecutive cytology results with negative HPV testing).[44]

In the country of the authors, classical cytology or liquid-based cytology (LBC) is recommended every 1–3 years, depending on the previous result in all women aged 25–69. However, during the pandemic period, it has been temporarily recommended to implement an HPV-dependent model, that is an isolated primary test for 14 high-risk HPV types (HRHPV14) or a combined test (co-testing) comprising a simultaneous HRHPV14 test and LBC with subsequent further diagnostic and therapeutic management depending on the test result.[45]

Clowry et al. in their study based on a questionnaire survey evaluated the cervical screenings' uptake in a group of 104, 25-60-year-old female patients from Ireland on at least one systemic immunosuppressive agent for a chronic inflammatory dermatological condition (85% of the enrolled were psoriatic patients). Of the screened population, 6% got abnormal results and 12.5% had a history of treatment for cervical dysplasia. Unfortunately, the study did not report data on the presence of HPV infection in the study group. The authors of the study emphasize the 85% screening rate (national programme) among the study participants, which was significantly higher than the national average of nearly 70%, and the important role of dermatologists in promoting cervical screening, especially among immunosuppressed female patients.[46]

SUMMARY

Due to the high prevalence of HPV infection, it is important to assess the most accessible treatment for psoriatic patients with an active infection. The choice should be made on the patient's gender, age, preferences, in order to achieve the best therapeutic effect.

Among the conventional drugs used in systemic therapy, acitretin seems to be safe based on systematic reviews and expert consensus. The not recommended drug with the potential to increase HPV replication is cyclosporine. The data on methotrexate is ambiguous. Apremilast and other small molecules have not been reported on regarding psoriasis and HPV treatment, similarly to DMF – more data is needed.

In the group of biological drugs, TNF-alpha inhibitors seem to be safe; however, there have been case reports showing results of HPV infection exacerbations and thus may require more trials. Based on the limited data available, IL17 antagonists (secukinumab) appear to be safe and promising as potential drugs of choice for these two comorbidities, while IL12/IL23 inhibitors (ustekinumab) might not be recommended, but more investigation on larger groups of patients is needed. Research on new drugs, such as IL23 inhibitors, is lacking.

The authors are aware that this review was limited by the lack of data with high levels of evidence. The majority of the analysed papers described case reports or case series. Considering the variety of new biological drugs, there will be more data about the discussed diseases, and the new possible findings may create an opportunity to publish official recommendations for psoriatic patients with HPV infection.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

ETHICS STATEMENT

The authors confirm that this material is original and has not been published in whole or in part elsewhere; that the manuscript is not currently being considered for publication in another journal; and that all authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

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