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INVESTIGATIVE REPORT

Anogenital Human Papillomavirus Prevalence is Unaffected by Therapeutic Tumour Necrosis Factor-alpha Inhibition

Alessandra HANDISURYA[1#], Stefanie LÁZÁR[1,2#], Pavol PAPAY[4], Christian PRIMAS[3], Andrea HAITEL[5], Reinhard HORVAT[5], Adrian TANEW[1], Harald VOGELSANG[3] and Reinhard KIRNBAUER[1]

Departments of [1]Dermatology, [3]Internal Medicine III, Division of Gastroenterology and Hepatology and [5]Pathology, Medical University Vienna, [2]Neurological Department Rosenhuegel, General Hospital Hietzing, and [4]Department of Internal Medicine, St. Elisabeth Hospital, Vienna, Austria

[#]These authors contributed equally to this paper.

Patients receiving tumour necrosis factor alpha (TNF-α) inhibitors are at increased risk of exacerbation of (myco-)bacterial and some viral infections. However, information on anogenital human papillomavirus (HPV) infection in these patients is sparse or conflicting. In this study 222 patients with psoriasis or inflammatory bowel disease (IBD), who received either anti-TNF-α inhibitors or alternatives (purine-, folic acid analogues, phototherapy, fumaric ester, mesalazine) continuously for at least 6 months, were evaluated for the presence of anogenital HPV-induced lesions, mucosal HPV DNA, and serological status of mucosal low-risk HPV6 and high-risk HPV16/HPV18. Hallmarks of anogenital HPV infection were more frequently detected in patients with psoriasis than in those with IBD. HPV-induced lesions, viral DNA, and seroprevalence were not elevated in participants with psoriasis or IBD, who received TNF-α inhibitors for a mean duration of 31.4 months (range 6–96 months) compared with recipients of alternative or no treatment. TNF-α blockade for a mean period of 31.4 months does not increase detectable anogenital HPV infection or disease. ***Key words: human papillomavirus (HPV); tumour necrosis factor-alpha; psoriasis; inflammatory bowel disease; anogenital infection; HPV seroprevalence.***

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Alessandra Handisurya, Department of Dermatology, Medical University Vienna, Waehringer Guertel 18–20, AT-1090 Vienna, Austria. E-mail: alessandra.handisurya@meduniwien.ac.at

Anogenital infection with mucosal human papillomaviruses (HPV) is the most common sexually transmitted viral disease worldwide; approximately 70% of sexually active men and women become infected during their lifetime (1). Mucosal high-risk HPV cause all cervical, most anal, and a subset of vulvar, vaginal, penile and oropharyngeal carcinomas (2). Low-risk HPV are responsible for the development of anogenital warts and laryngeal papillomas.

Inhibition of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) is used for the treatment of chronic immune-mediated inflammatory diseases, including psoriasis and inflammatory bowel disease (IBD). However, TNF-α blockade increases the risk of acquisition and/or reactivation of certain (myco-) bacterial, fungal, and viral infections, in particular infection with *Mycobacterium tuberculosis*, hepatitis B, and varicella zoster virus (3, 4). Reports on an association between anogenital HPV infection and TNF-α inhibition are sparse. A few case reports were published on the (re-)occurrence of anogenital warts in patients shortly after initiation of anti-TNF-α therapy (5–7). These patients developed extensive anogenital lesions within the first 4 months of TNF-α blockade and were treated successfully with standard cryotherapy. Interestingly, no relapse of wart formation was observed after discontinuation of anti-TNF-α treatment. The few studies on cervical cytopathology, as a marker of HPV infection, are restricted to patients with IBD receiving immunomodulatory agents, including the anti-TNF-α monoclonal antibody infliximab, and have conflicting results. While some studies did not find a significant association between cervical abnormalities and the use of immunomodulators in patients with IBD (8–10), others reported a higher risk of the development of cervical pathologies in women with IBD receiving immunomodulators, including infliximab, purine analogues, methotrexate, and prednisone (11). Furthermore, combination therapies with multiple immunosuppressants or prolonged treatment periods were found to contribute to the increased risk (11). In females with Crohn's disease, anti-TNF-α therapy was associated with a higher risk of cervical dysplasia compared with a healthy control population (12). Recently, female patients with rheumatoid arthritis were prospectively investigated for the presence of high-risk mucosal HPV infection, represented by HPV DNA and cervical cytopathology, prior to and at 6 months of anti-TNF-α treatment (13). After this relatively short period of TNF-α blockade, HPV infection remained unchanged in the majority of recipients and none developed visible lesions, suggesting that 6 months of therapy do not strongly influence the outcome of high-risk HPV infection and disease. Furthermore, no elevated risk of infection was observed compared with healthy controls.

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Despite divergent observations in the available studies, it is possible that immunomodulatory agents, in particular TNF-α blockers, can contribute to an increased susceptibility to anogenital HPV infection, elevate the risk of persistent infection and associated disease due to delayed or failing viral clearance, or lead to reactivation and/or exacerbation of latent infection, especially after long-term administration.

The aims of this study were to investigate a possible association between TNF-α inhibition and anogenital HPV infection, and to compare patients with psoriasis or IBD who were receiving TNF-α inhibitors with recipients of alternative or no therapies.

METHODS

This prospective, open, controlled observation study with cross-sectional analysis was approved by the Institutional Review Board of the Medical University of Vienna. Participants, who gave written informed consent, were 18–80 years of age with a history of psoriasis or IBD, namely Crohn's disease and ulcerative colitis, and at enrolment had received at least 6 months of continuous treatment regimen. Psoriasis was graded using the Psoriasis Area and Severity Index (PASI) according to the formal European consensus (14), Crohn's disease activity was determined using the Harvey-Bradshaw-Index (mild: ≤ 7; moderate–severe: ≥ 8) (15), and ulcerative colitis was categorized using the partial (non-invasive) Mayo score (mild: ≤ 4; moderate–severe: > 4) (16). Patients were assigned to subgroups according to their current therapy: (*i*) TNF-α inhibitor monotherapy; (*ii*) monotherapy with purine or folic acid analogues, e.g. azathioprine, 6-mercaptopurine, methotrexate; (*iii*) combination therapy with TNF-α blocker plus purine or folic acid analogues; (*iv*) alternative, such as phototherapy, fumaric acid, mesalazine, or no therapy. Information about illness duration and severity, current and former disease-related medical treatments, smoking habits, and sexual history with emphasis on pre-existing HPV infection were obtained.

Mucosal HPV DNA was assessed in swab samples ($n = 2$ for males; $n = 3$ for females) taken at study enrolment from the penis, vulva, cervix, and perianal region using the Digene Hybrid Capture 2 (hc2) kit (Qiagen, Gaithersburg, MD, USA). This assay detects the presence of one or more HPV types belonging to the group of high-risk HPV (represented by HPV16/18/31/33/35/39/45/51/52/56/58/59/68) and/or to the group of low-risk HPV (represented by HPV6/11/42/43/44), but cannot discriminate which individual mucosal HPV type(s) is or are present in the sample and is not suitable for detection of cutaneous HPV. Testing was performed according to the manufacturer's instructions (cut-off: 1 relative light unit (pg/ml) equivalent to 100,000 HPV copies/ml). Cervical Papanicolaou (PAP) smears were collected by cytobrush and graded according to the Bethesda system. For the detection of neutralizing HPV-specific antibodies in patients' sera, the *in vitro* pseudovirion (PsV)-based standard neutralization assays were employed (17). HPV16 and HPV18 were chosen as representatives for high-risk, HPV6 for low-risk types. Sera were tested at dilutions of 1:10 to 1:40 as published previously (18). All assay procedures were performed by laboratory personnel blinded to the patients' history including diagnosis and therapy, to minimize variability and bias of the results.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 15.0. Differences in infection rates were calculated by Mann-Whitney *U* or Pearsons's χ^2 test (2-sided asymptotic significance), when applicable. *p*-values < 0.05 were statistically significant.

RESULTS

A total of 222 patients with psoriasis or IBD, who had received their current medication continuously for at least 6 months, were enrolled. At inclusion, the severity of the underlying diseases, psoriasis and IBD, were evaluated and graded into mild or moderate–severe. The demographic characteristics of the study participants are given in Table I. For study analyses, the cohort was stratified into 4 groups according to their current therapies (Table I). The mean duration of therapeutic TNF-α inhibition was 39.2 months for psoriasis, 23 months for IBD patients, and 31.4 months (range 6–96 months) for both populations. There were no statistically significant differences in age ($p = 0.318$) or sex ($p = 0.071$) between individual treatment groups. On average, each patient reported 11.5 sexual partners (range 0–101). Interestingly, patients with psoriasis had statistically significantly more lifetime sexual partners compared with patients with IBD ($p = 0.040$), but they did not differ in their smoking habits ($p = 0.171$). The number of lifetime sexual partners and smoking status did not differ significantly between the 4 treatment groups (not shown).

At time of enrolment, anogenital warts were observed in 2.7% (6/222) of all participants (Table II). However, condylomata were not associated with anti-TNF-α therapy ($p = 0.753$), as distribution was equal between recipients of TNF-α blockers and other treatment modalities. No cervical lesions were observed macroscopically

Table I. *Demographics of patients*

	Psoriasis ($n = 113$)	IBD ($n = 109$)
Sex, %		
Female	31.9	47.7
Male	68.1	52.3
Age, years, mean (range)	48.4 (21.7–79.3)	42.4 (19.4–70.9)
Severity of disease, %		
Mild	90.2	90.8
Moderate	8	6.4
Unknown	1.8	2.8
Treatment groups, %		
TNF-α inhibitors	47.8	45.9
Purine/folic acid analogues	0	24.8
Combination therapy	0.9	5.5
Alternative/no medication	51.3	23.9
Personal status, %		
Relationship	63.7	76.1
Single	36.3	23.9
Number of sexual partners, %		
<10	48.7	68.8
10–19	15	20.2
≥20	19.5	10.1
Unknown	16.8	0.9
Smoking status, %		
Current	40.7	29.4
Former	19.5	21.1
Never	38.1	48.6
Unknown	1.8	0.9

IBD: inflammatory bowel disease. TNF-α: tumour necrosis factor-α.

in the female participants. The treatment period in the 3 affected TNF-α recipients was shorter than the mean duration of 31.4 months for the entire cohort, namely 18, 21, and 23 months, respectively. After stratifying for disease, warts were more frequently observed in psoriasis (1.8%; 4/222) than in IBD patients (0.9%; 2/222), but the results were not statistically significant ($p=0.434$).

When the infection rate, as represented by the presence of HPV DNA, was analysed for the treatment groups, no statistically significant differences were observed ($p=0.779$) (Table II). While the detection rate for overall mucosal HPV DNA in recipients of TNF-α inhibitors was slightly higher compared with participants of the purine or folic acid analogues group, recipients of combination therapy and of alternative or no therapy showed comparable rates. When results were evaluated according to high-risk or low-risk HPV DNA, no statistically significant differences were observed between the numbers of high-risk HPV DNA-positive participants in the TNF-α inhibitor group, the purine or folic acid analogues group, or the alternative/no therapy group. Similarly, the numbers of low-risk HPV DNA positives did not differ significantly between these groups. While 28.6% of the individuals under combination therapy had detectable high-risk as well as low-risk HPV DNA, this trend for augmented prevalence was not significant and may be regarded with caution due to the small number of subjects.

In addition, we obtained PAP smears from 88 women to investigate the risk of cervical neoplasia. Two smears yielded non-interpretable results and were not repeated due to lack of follow-up visits. The vast majority (85/86) showed normal cervical cytology and thus no significant differences were found between the individual treatment groups ($p=0.654$). One patient was diagnosed with high-grade squamous intraepithelial lesion and immediately referred to a gynaecology clinic. This 31-year-old patient had had mild ulcerative colitis for 5 years, and had been receiving adalimumab for the past 2 years. The patient reported 6 lifetime sexual partners and had given up smoking prior to initiation of anti-TNF-α therapy.

We next sought to determine previous exposure to mucosal HPV (Table III), as viral DNA testing detects current, but not past HPV infections that may have already been cleared by the host's immune system. Overall HPV seropositivity and seropositivity against each individual HPV type tested were lower throughout in recipients of TNF-α inhibitors compared with the control group that received alternative or no treatments. This also accounted for seropositivities against both high-risk types and all 3 tested types combined, which were higher in the controls, albeit not statistically significant. The lowest rates were generally found in the group receiving purine or folic acid analogues. Combination therapy did not significantly increase seropositivity; however, the low number of patients in this cohort, and the fact that HPV-specific antibodies are generated after a latency period, may hamper definitive conclusions.

To analyse the impact of sexual behaviour on HPV infection, patients were stratified into 3 groups according to the cumulative numbers of sexual partners. As expected, detection of HPV DNA significantly correlated with increasing numbers of lifetime partners ($p=0.023$) (Table SI[1]). In addition, patients with more sexual partners displayed higher viral loads, although the results were not statistically significant ($p=0.079$) (not shown). Unexpectedly, no significant correlation could be found between the total number of lifetime sexual partners and HPV seropositivity (Table SI[1]).

Our data further support the impact of smoking on HPV infection (Table SI[1]). Current smokers significantly ($p=0.003$) more often had detectable HPV DNA at any site tested, compared with former and non-smokers. Whether this observation is due to diminished capability of smokers to clear HPV infection or due to increased acquisition by riskier lifestyle compared with non-smokers is unclear. HPV seropositivity between groups with different smoking habits showed no significant differences (Table SI[1]).

Surprisingly, when the HPV DNA detection rates were correlated with the underlying disease, patients with psoriasis showed a tendency for more frequent anogenital HPV infection than patients with IBD (31.9% vs. 21.1%; $p=0.070$) (Table SI[1]). This tendency was also observed

Table II. *Comparison of human papillomavirus (HPV) DNA prevalence between different treatment groups*

	TNF-α inhibitors ($n=104$) % (n)	Purine/ folic acid analogues ($n=27$) % (n)	Combination therapy ($n=7$) % (n)	Alternative/ no medication ($n=84$) % (n)
Anogenital warts	2.9 (3)	0 (0)	0 (0)	3.6 (3)
Any HPV DNA	26.9 (28)	18.5 (5)	28.6 (2)	28.6 (24)
High-risk HPV DNA	17.3 (18)	11.1 (3)	28.6 (2)	19.0 (16)
Low-risk HPV DNA	19.2 (20)	14.8 (4)	28.6 (2)	14.3 (12)

TNF-α: tumour necrosis factor-α.

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Table III. *Seroprevalence against mucosal human papillomavirus (HPV) in different treatment groups*

Seropositivity	TNF-α inhibitors ($n=104$) % (n)	Purine/ folic acid analogues ($n=27$) % (n)	Combination therapy ($n=7$) % (n)	Alternative/ no medication ($n=84$) % (n)
Any HPV-type	22.1 (23)	14.8 (4)	14.3 (1)	29.8 (25)
α-HPV 6	11.5 (12)	3.7 (1)	14.3 (1)	16.7 (14)
α-HPV 16	10.6 (11)	7.4 (2)	14.3 (1)	11.9 (10)
α-HPV 18	6.7 (7)	3.7 (1)	0 (0)	11.9 (10)
α-HPV 16 or 18	14.4 (15)	11.1 (3)	14.3 (1)	19.0 (16)
α-HPV 16 and 18	2.9 (3)	0 (0)	0 (0)	4.8 (4)
α-HPV 6, 16 and 18	0 (0)	0 (0)	0 (0)	2.4 (2)

TNF-α: tumour necrosis factor-α.

for high- and low-risk HPV. High-risk HPV DNA was detected in 21.2% of psoriasis compared with 13.8% in patients with IBD ($p=0.143$), low-risk HPV DNA in 20.4% of psoriasis vs. 13.8% of patients with IBD ($p=0.192$). Disease severity of both, psoriasis and IBD, did not correlate with DNA status ($p=0.605$). The HPV prevalence pattern has been reported to differ between sexes and to decrease with age among women, but not among men (19). Since in our study cohort the distribution of men and women varies between underlying diseases, for instance, in the psoriasis group men were more frequently represented, while in the IBD group the number of men and women was almost equally distributed, we compared the HPV DNA results separately according to sex in both patient groups. In patients with psoriasis, women more frequently harboured mucosal HPV DNA than men, albeit the results were not statistically significant. Overall HPV detection rates were lower in men than in women (28.6% and 38.9%, respectively, $p=0.273$). Similarly, high-risk and low-risk HPV DNA were less frequently found in psoriatic men (18.2% for both) than in women (27.8% and 25%, respectively) ($p=0.245$ for high-risk and $p=0.402$ for low-risk HPV DNA analyses). An analogous trend was observed in patients with IBD after evaluation of current infection according to sex. Overall, HPV DNA was less frequently detectable in men compared with women (19.3% vs. 23.1%, respectively, $p=0.629$). Analysis of high-risk and low-risk HPV in the IBD group revealed detection rates in men of 15.8% and 8.8%, respectively, and women of 11.5% and 19.2%. However, results were not statistically significant ($p=0.520$ and $p=0.113$, respectively).

Similar to the DNA results, seropositivity to any HPV type tested was more frequently present in patients with psoriasis (26.5%) than in those with IBD (21.1%). In particular, neutralizing antibodies against high-risk HPV16 were significantly more often detected in patients with psoriasis than in those with IBD (15.0% vs. 6.4%; $p=0.039$). Neutralizing antibodies against HPV6, HPV18, both HPV16/18 ($p=0.061$), and all 3 tested types combined were also more frequently observed in patients with psoriasis, but the results were not statistically significant.

DISCUSSION

Biologicals targeting TNF-α have emerged as an efficient therapeutic strategy for chronic immune-mediated diseases that often require long-lasting immunomodulatory therapies. However, due to their relatively recent development, long-term safety profiles have not been fully determined. In contrast to the awareness of an increased susceptibility for tuberculosis and hepatitis B virus infection under TNF-α blockade (20–24), knowledge about the risk of anogenital HPV infection is limited and controversial data exist (23, 24). Herein, we investigated present and past anogenital HPV infection in patients with psoriasis or IBD, and demonstrated that TNF-α inhibition does not increase the prevalence of anogenital HPV infection and disease after more than 30 months of treatment, compared with other immunomodulatory or no treatment.

In the available case reports, patients developed extensive anogenital lesions within the first 4 months of TNF-α blockade and were successfully treated (5–7). Interestingly, no relapse was observed after discontinuation of anti-TNF-α treatment. While the majority of patients denied previous HPV-associated diseases, one reported having anogenital warts more than 10 years ago (5). Whether the re-occurrence is attributable to newly acquired infection or exacerbation of latent infection is unknown. The few studies on abnormal cervical cytology and dysplasia in association with TNF-α blocker therapy in patients with IBD showed conflicting results (8–12). While some studies did not find a significant association (8–10), others reported a higher risk of the development of cervical pathologies under therapy with immunomodulators, including infliximab, purine analogues, methotrexate, and prednisone (11, 12, 25). A major difference between these studies and ours is that, herein, patients with psoriasis were additionally investigated. More importantly, to rule out any effects of the underlying pathological condition, patients in the TNF-α inhibitor group were compared with patients with the same disease who received alternative or no therapy as appropriate controls, rather than a healthy control population. In particular, IBD *per se* was reported to pose an independent risk factor for the development of cervical pathologies (9–11, 25, 26). In a recently published study, no elevated risk of mucosal HPV infection, represented by HPV DNA and cervical cytopathology, was observed in female patients with rheumatoid arthritis, prior to and at 6 months of anti-TNF-α treatment compared with healthy controls (13). In our study cohort, participants had received TNF-α agents continuously for at least 6 months, the mean treatment duration was 31.4 months, and the longest period encompassed 96 months of intervention. While the observational period here is considerably longer than in comparable studies, still, no conclusions about the safety of long-term use of anti-TNF-α therapies can be drawn, since HPV-induced neoplasia may develop over years of persistent infection, and more studies investigating patients after years of treatment are warranted. Furthermore, we could not stratify the TNF-α inhibitor group into individual substances, as study size did not provide sufficient power to address this question. The prevalence of varicella zoster virus infection was reported to be higher in patients receiving infliximab compared with etanercept (27, 28), thus it would be interesting to compare anogenital HPV prevalence and the use of individual anti-TNF-α agents. The data presented herein show that the use of TNF-α blockers in patients with psoriasis or

IBD for more than 30 months does not increase the risk of anogenital HPV infection and disease, and thus seems to have an acceptable safety profile. These results are of clinical importance, reassuring the use of these effective biologics in patients with high need.

An intact cellular immune system is required to control papillomavirus infection and disease. Experimental proof of the crucial role of T cells was demonstrated recently in a murine model for papillomavirus infection, in which persistent infection and papilloma development were observed in immunocompetent animals only after selective T-cell removal (29), or in athymic mouse strains lacking T cells (29, 30). In humans, compelling evidence has emerged from human immunodeficiency virus-infected individuals and immunosuppressed transplant recipients, who are at increased risk of developing HPV-induced anogenital malignancies, cutaneous warts, or non-melanoma skin cancers, the latter possibly being attributable (at least in part) to infection with cutaneous HPV types of genus beta (beta-HPV) (31–34). In some congenital disorders, abnormal susceptibility to skin and mucosal HPV infection was linked to distinct cellular immune defects (35–37). In psoriasis, the underlying dysregulation of T cells may also impair control and efficient elimination of cutaneous and/or mucosal HPV. Previously, beta-HPV have been detected in patients with psoriasis in a remarkably high frequency, raising questions about a possible causative role of, or a specific permissiveness for, these types (38, 39). A recent study in patients with psoriasis receiving TNF-α blockers did not find an increased prevalence of beta-HPV, compared with methotrexate or no treatment (40). However, the data from the current study demonstrated a trend for more frequent HPV-induced anogenital lesions, increased prevalence of mucosal HPV DNA, and significantly higher seropositivity to high-risk HPV16 in psoriasis. Whether these results merely reflect cumulative lifetime sexual partners or increased acquisition and/or diminished clearance of infection remains unclear. In addition, sex-specific differences in HPV prevalence were reported (19). Analysis of prevalent HPV infection separately for males and females with psoriasis revealed more frequent infection in females, although the results were not statistically significant. For females with psoriasis the observed trend for higher prevalence of mucosal HPV infection compared with males should be regarded with caution, due to the limited number of participants in our study cohort, and warrants further investigation in a larger population. Nevertheless, closer monitoring, lifestyle recommendations, and, possibly, timely vaccination seem advisable.

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