

Prevalence of cervical HPV and attitude towards cervical screening in IBD patients under immunomodulatory treatment: a multidisciplinary management experience

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Abstract. – **OBJECTIVE:** Therapeutic strategies for Inflammatory Bowel Diseases (IBD: Crohn's disease and Ulcerative Colitis) have improved but the risk for HPV infection in patients under immunomodulatory/biologic treatment is unclear. Objective of the study is to identify the attitude of patients and caregivers to cervical screening. To determine the prevalence of HPV and cervical lesions in IBD patients receiving immunomodulatory/biological treatment.

PATIENTS AND METHODS: IBD patients treated with immunomodulators were enrolled from November 2016 to September 2017, thanks to a multidisciplinary cooperation. A survey was administered to enrolled patients as well as to a selected network of IBD expert physicians. Patients who consented underwent gynecological examination, smear, HPV DNA test, colposcopy, vaginal and cervical microbiological swabs.

RESULTS: 294 patients from AMICI Onlus Association, 119 patients from the hospital clinic, 30 doctors from national IBD centers participated to the survey. 19 patients from the IBD clinic underwent cervical screening. More than 90% of doctors consider their patients at risk of cervical cancer. A low prevalence of high-risk genotypes and related HPV lesions and an increased prevalence of bacterial vaginosis emerged in the studied population.

CONCLUSIONS: Biological drugs could lead to a positive immunomodulation towards HPV infection. In IBD patients an alteration of the vaginal and intestinal microbiota seems to be coexisting.

Key Words:

Inflammatory bowel disease (IBD), Cervical cancer, HPV, Immunomodulation, Screening.

Introduction

Cervical cancer is caused by a viral infection and, consequently, immunosuppressed women, including organ transplant recipients and those with systemic lupus erythematosus, have an increased risk of cervical abnormalities. Whether the risk of cervical abnormalities is increased similarly in women with inflammatory bowel disease (IBD), which often is treated with immunosuppression, is unknown and still a matter of research and debate¹⁻¹¹.

Although 2 recent reports showed an increased risk of cervical abnormalities in women with IBD, another observational study found no significant difference^{1,5-7}. Their results may not be generalizable because the enrolled patients were recruited from tertiary care referral IBD centers; the differences in the results may have been owing to differences in the demographics of the subjects between the different study sites. A previous population-based investigation suggested no increased risk for cervical cancer in IBD; however, lesser degrees of neoplasia were not evaluated.

The recommended screening interval between examinations for average-risk women with normal Papanicolaou's (Pap) smears is 2-3 years⁸⁻¹⁰. However, women with immunosuppression, such as those with human immunodeficiency virus infection or history of organ transplants, are recommended to attend screening every year⁹. Currently, there are no specific univocal recommendations for wom-

en with IBD, even though many are exposed to immunosuppressive medications during the course of their disease. Moreover, many IBD patients are not well aware of their potentially increased risk of cervical cancer with heterogeneous attitudes toward screening and suboptimal attendance reported in different researches^{2,12-18}.

Patients and Methods

This was a prospective, cross-sectional study, which was performed from November 2016 to September 2017 in a University Hospital setting at Fondazione Policlinico Gemelli IRCCS – UCSC Rome thanks to the multidisciplinary cooperation between the IBD gastroenterology clinic and the Lower genital tract disease clinic. Both the clinics are referral centers in Italy for the above-mentioned diseases.

A self-designed survey was conducted in a cohort of female IBD patients treated within the Hospital IBD clinic and at the same time in a cohort of patients treated in other centers registered all over Italy within a national patients' network (AMICI ONLUS Association). The survey also enclosed an anamnestic questionnaire with demographic data, questions regarding cervical smear test frequency and adhesion to screening, HPV vaccination and knowledge about HPV and HPV related lesions. Patients completed the survey with a physician present to help questions understanding. The aim was to test IBD patients' knowledge and attitude about cervical screening, HPV, cervical cancer and pre-cancer. Pregnant patients, HIV, HBV, HCV positive patients, were excluded from the study.

A self-designed anonymous survey by electronic link was also run within a national network of physicians – junior trainees and seniors – involved in IBD care all over Italy following a personal invite from the authors of the present paper, with the aim to assess their management of cervical screening and HPV in IBD patients.

Further and complementary clinical information was collected and then obtained from the patients' case notes.

This project, part of a more complex investigation, has been approved by Ethical Committee of University of the Sacred Heart of Rome (Protocol No. P/491/CE/2011).

Results

294 patients belonging to the AMICI Onlus Association, 119 patients from the IBD university hospital clinic participated to the survey. 19 patients from the IBD university hospital clinic under treatment with biologic drugs accepted to undergo a gynecological examination including HPV testing, microbiological swabs, colposcopy and Pap smear that we called “intensive cervical screening”. The mean age of these women, the smoking status and their instruction level, as well as their IBD status, classification and features are described in Table I. Most of the patients at the time of the study resulted under steroids and/or treatment with mesalazine or other immunosuppressant agents. The great majority of patients also in the screening group were under multiple treatments, but 18 out of 19 actively under biologic drugs. Ongoing and past treatment status in the groups is described in Table II. From a gynecologic point of view, the anamnestic part of the survey submitted to these participants investigated their potential risk factors for HPV (like estro-progestinic pill use and age at first intercourse, together with smoking status), incidence of previous hpv occurrent infections and/or related treatments and incidence of previous other vaginal infections. The survey also investigated patients' attitude and attendance to screening (Pap smear and HPV testing). In the three groups, women declared to have been attending screening at least once in 89.9%, 85.4% and 94.7% of cases, respectively. The rate of abnormal smear in the three groups was respectively 16.8%, 18.9% and 21%. More than 30% of subjects in each group had HPV testing done. These results are summarized in Table III. Correlating and comparing data from our investigation with data on the general population collected by the National Women's Health Observatory, the IBD population attending our University Hospital clinic also compared to the population of the Association “AMICI Onlus” which represents the population affected by IBD followed in other national centers seem to have a greater adherence to screening with pap smear, even if the attendance rate results quite high and comparable between the 3 populations and is around 1-3 years (Figure 1).

From the results of the survey about HPV knowledge it can be observed that all patients have heard about HPV and are aware that there is a vaccine to prevent this infection. Moreover, they are aware that HPV can cause cervical can-

Table I. Main features of the enclosed patients.

	Patients from the University hospital IBD referral clinic	Patients from national network Associazione AMICI ONLUS	Patients included in the "intensive cervical screening" group	p-value
Number of patients (F)	119	294	19	
Patients > 35 years of age (%)	47.1% (56)	62.9% (185)	68.4% (13)	0.008
Crohn's disease	51% (61)	69.4% (204)	57.7% (11)	0.001
Ulcerative colitis	50.4% (60)	30.9% (91)	42.1% (8)	0.001
Duration of disease (DS)	9.6 (7.1)	13.1 (10.1)	9.3 (10.2)	Ns
Disease activity:				0.345
Remission	22.8% (27)	22.8% (67)	36.8% (7)	
Mild	21.1% (25)	15.0% (44)	15.7% (3)	
Moderate	33.9% (40)	38.23% (112)	42.1% (8)	
Severe	22.0% (26)	23.8% (70)	5.2% (1)	
Smoking habit	30.25% (36)	31.63% (93)	26.3% (5)	0.869
Number of cigarette smoked /day	100% < 10/day 0.00% > 10/day	46.1% (42) < 10/day 53.8% (49) > 10/day	100% < 10/day 0.00% > 10/day	
Instruction level				0.624
Primary school	17.1% (20)	21,5% (63)	26.3% (5)	
Secondary school	58.9% (69)	55.8% (163)	42.1% (8)	
University degree	23.9% (28)	22.6% (66)	31.6% (6)	

cer and that regular screening is one of the best ways to prevent the onset of preneoplastic alterations and cancer. On the other hand, especially patients from AMICI Onlus association were not fully aware of the possible ways of transmission and that HPV can cause other genital and non-genital neoplasms.

The survey's items and patients' knowledge about HPV are summarized in Figure 2. The survey submitted to the IBD specialists network showed that more than 90% (93%) consider their patients at risk of cervical cancer, 97% of them works in an IBD dedicated service and all of them are registered within at least 1 IBD scientific

Table II. Ongoing and past treatment status.

	Patients from the University hospital IBD referral clinic	Patients from national network Associazione AMICI ONLUS	Patients included in the "intensive cervical screening" group	p-value
Ongoing Treatment at Time of Study				
Steroids	30.6% (30)	30.3% (77)	64.7% (11)	0.012
Immunosuppressants	30.43% (29)	27.4% (63)	37.5% (6)	0.592
Mesalazin	63.4% (66)	66.0% (169)	60% (9)	0.823
Infliximab	15.9% (19)	13.9% (41)	42.1% (8)	0.005
Golimumab	8.4% (10)	0.68% (2)	21.05% (4)	0.000
Adalimumab	8.4% (10)	9.1% (27)	10.53% (2)	0.943
Vedolizumab	9.2% (11)	7.4% (22)	10.5% (2)	0.775
Ustekimumab	1.6% (2)	1.0% (3)	10.5% (2)	0.006
Previous Treatments				
Steroids	90.0% (100)	89.57% (249)	100% (19)	0.334
Immunosuppressants	60.6% (54)	55.9% (131)	88.8% (16)	0.022
Mesalazin	95.3% (103)	92.59% (250)	90% (17)	0.332
Infliximab	29.4% (35)	30.9% (91)	47.3% (9)	0.287
Golimumab	4.2% (5)	0.34% (1)	10.53% (2)	0.000
Adalimumab	5.8% (7)	0.34% (1)	5.26% (1)	0.884
Vedolizumab	8.4% (10)	9.1% (27)	10.53% (2)	0.001
Ustekimumab	2.5% (3)	0.34% (1)	5.26% (1)	0.040

Table III. Gynecological history of patients.

	Patients from the University hospital IBD referral clinic	Patients from national network Associazione AMICI ONLUS	Patients included in the "intensive cervical screening" group	p-value
Patients (No.)	119	294	19	ns
Age at first inter-course (years) (± SD)	18.25 ± 2.90	18.8 ± 2.70	19.6 ± 3.04	ns
Estro-progestinic pill use	44.54% (53)	45.2% (113)	36.84% (7)	
Duration				
< 5 years	58.49% (31)	47.1% (63)	57.1% (4)	0.775
> 5 years	41.51% (22)	52.9% (71)	42.9% (3)	0.345
Previous HPV infection and/or cervical treatment	21.74% (25)	20.92% (58)	63.15% (12)	0.001
Previous vaginal infection	62.5% (75)	61.1% (180)	47.36% (9)	0.378
Patients that attended screening at least once (Pap smear)	89.9% (107)	85.4% (251)	94.7% (18)	0.273
Timing of Attendance Declared				
- Yearly	29.52% (31)	27.46% (81)	33.3% (6)	
- 1-3 years	53.33% (56)	49.8% (123)	38.8% (7)	
- 1-5 years	17.1% (18)	17.4% (43)	27.7% (5)	
Abnormal Pap smear	16.8% (20)	18.9% (48)	21.0% (4)	0.824
- Ascus-L-SIL	55.0% (11)	16.0% (8)	0%	
- HSIL	10% (2)	6.0% (3)	0%	
- Other	35.0% (7)	78.0% (37)	100% (4)	
HPV test:	37.82% (45)	35.3% (104)	31.6% (6)	0.040
- Done	12.5% (6)	16.22% (18)	42.86% (3)	0.127
- Positive	HR 2.52%	HR 9.13%	HR 15.79%	
- Genotypes	LR 2.52%	LR 47.27%	LR 57.89%	

society. The majority of the clinicians enclodes gynecological screening in the management of IBD under treatment, respectively 87,5% when under immunosuppressants and 83,7% when un-

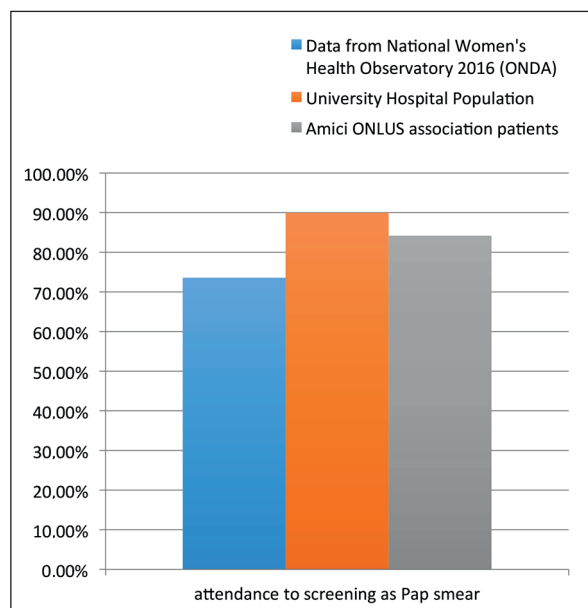


Figure 1. Attendance and compliance to screening.

der biologic drugs. On the other hand, just 33% has an organized gynecologic screening pathway for patients in the clinic.

In the group of 19 patients attending the university hospital clinic, who underwent active cervical screening 42.1% were positive for HPV, 33% with a high-risk genotype. All smears were normal for HPV related lesions and the positive colposcopies (31.5%) were likely to be low-grade lesions. Swabs reported a significant incidence of bacterial vaginosis (47.36%) with prevalence of *Streptococcus agalactiae* (44%) *Mycoplasma* (44%) and *Gardnerella* (12%), showing an altered vaginal microbiota as a possible consequence of the altered bowel microbiota (Figure 3).

Discussion

Data from the survey shows that IBD patients, attending regularly an IBD clinic are quite well aware about HPV, HPV vaccine and oncologic risk, but not fully aware about possible transmission routes and role of Pap smear testing, with better awareness outcome in patients attending the University Hospital clinic compared to AMI-

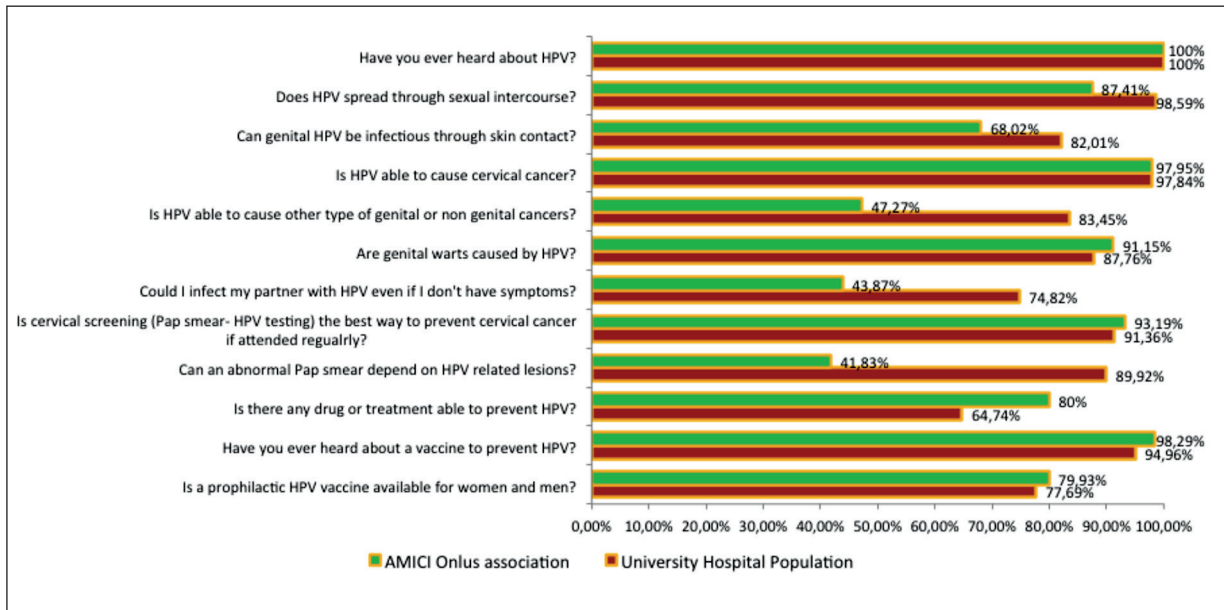


Figure 2. Survey's items and patients' knowledge about HPV and screening in the two studied groups.

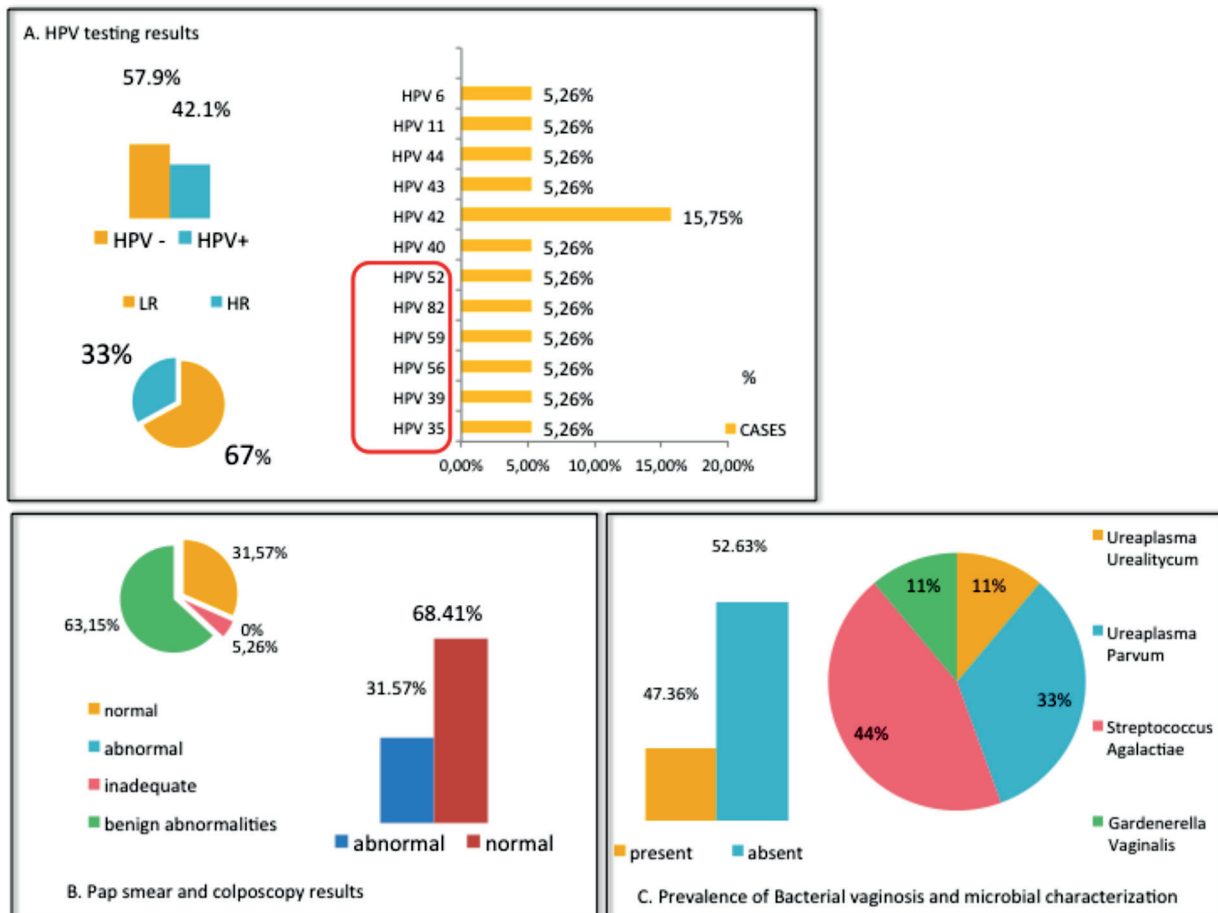


Figure 3. Results from the subgroup that underwent "intensive cervical screening".

CI Onlus association, which represents other national non-tertiary referral IBD centers. Our results show that the studied IBD female population seem to be well compliant to cervical screening, if compared to general population.

Results from the survey submitted to a national network of IBD clinicians underline that most of them consider IBD female population at high risk for HPV infection and cervical cancer, although a few of them seem to have an organized gynecological and cervical screening protocol in their IBD clinic.

This multidisciplinary approach including a gynecological screening in female IBD patients shows how their standard of care could be improved, also helping them being more aware of HPV infection risks and the importance of cervical screening.

Although the number of patients actively screened in the study is small, it reflects and well represents the female IBD population. In this group of women HPV positivity prevalence is higher than in the general population, but with a high prevalence of Low Risk (LR) and uncommon genotypes. Surprisingly all the smear tests were normal with a low rate of colposcopy findings, because of faint low-grade lesions. The role of biologic drugs on risk of cervical cancer is still not clear and very debated, and our data, even if on a small population, seem to reveal some kind of “positive immunomodulation” from biologic drugs that could temporarily or partially balance the increased risk due to the immunosuppressive action of most of the other treatments administered for IBD.

What emerged from the smears and swabs results is a high rate of Bacterial vaginosis as if the vaginal microbiota was as altered as the bowel microbiota.

Some reports¹⁹⁻²² have underlined how an altered vaginal microbiota is probably fundamental background to HR-HPV infection and to the carcinogenic process.

Finally, our study underlines how crucial and feasible is, both for IBD patient’s clinical management and knowledge, a multidisciplinary approach including also gynecologic consult and cervical screening, especially in a referral center.

Nevertheless, there are some limitations. First of all, the patient population enrolled is limited as this was meant to be a pivotal trial. Secondly the questionnaire dedicated to physicians was sent to a private Italian network of IBDologists which is not a real expression of the national society

for IBD, which will address, on the base of this experience a more robust national survey. Finally, patients are not stratified for type of disease or type of treatment or year of exposure to the immunomodulatory/biological drug because of the limited number and also because that was not the main focus of this single center study.

Conclusions

Larger follow-up and immunological studies could better help understanding the role of the different IBD treatments, especially biologic drugs and immunomodulators, on HPV infection and clearance and on cervical cancer risk, as this matter still remains unclear as well as difficult to manage due to the long history of multiple treatments.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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