

Does Fingolimod Increase the Risk of Developing Human Papillomavirus (HPV) Related Cancers: A Case Series

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Objective

To describe five cases of possible HPV reactivation or increased risk of dysplasia in women taking fingolimod.

Background

- There is currently no data demonstrating a connection between fingolimod and development of HPV-related cervical dysplasia.
- HPV prevalence is 50% for sexually active men and women.
- Human papillomavirus (HPV) infections are responsible for approximately 90% of cervical cancers and other HPV-related anogenital cancers.
- The peak age for HPV infection is in the early 20s, leading to a peak prevalence of HSIL around age 30, with the highest cancer risk at ages 45 to 60.
- 9/10 HPV infections will go away by themselves in two years.
- Fingolimod is a commonly used treatment for relapsing remitting multiple sclerosis. It is a S1P receptor modulator that suppresses the egress of lymphocytes from the lymph nodes reducing the number of lymphocytes in peripheral circulation.
- The exact mechanism of action of fingolimod in patients with multiple sclerosis is unknown.
- There is an increasing body of evidence demonstrating that sphingosine 1-phosphate (S1P) is involved in cancer surveillance.
- S1P regulates processes such as inflammation, which can drive tumorigenesis and neovascularization, which provides cancer cells with nutrients and oxygen leading to cell growth and survival.
- A study done by Ricklin, et al. (2013) concluded patients treated with fingolimod show a slightly reduced antiviral T-cell response. This reduced response is accompanied by a subclinical reactivation of VZV or EBV in the saliva of 20% of patients

Methods

- A retrospective chart review of five women with MS treated with fingolimod and known HPV with varying degrees of cervical or vulvar dysplasia.
- Retrospective chart review of five female patients at the University of Colorado Neuroimmunology clinic

Case Studies

- Case 1:** 57 yo F with MS on fingolimod since 2011 with HPV-related cervical dysplasia. History includes HPV+ pap test in 2001 with HPV clearance until 2015 when pap test results showed cervical LSIL and high-risk HPV, followed by HSIL/CIN 2 in 2016. Patient had colposcopy and LEEP and discontinued fingolimod in 2016 due to progression of dysplasia.
- Case 2:** 45 yo F with MS on fingolimod since 2013. History includes abnormal pap testing beginning at age 18, year 1990. HPV status unknown this time. She underwent colposcopy and repeated Pap in 6 months with normal results with subsequent normal paps until 2015 when she was HPV positive, requiring a colposcopy and LEEP, showing CIN grade 1. In 2016 she elected to proceed with hysterectomy for cervical dysplasia and pelvic pain. Pathology confirmed CIN, grade 2 after surgery.
- Case 3:** 28 yo F with MS on fingolimod since 2015 with HPV-related vulvar dysplasia. History includes HPV + pap test and genital warts in 2014. Subsequent pap test results in 2016 showed high risk HPV and vulvar HSIL/VIN 3. Patient had colposcopy, laser ablative therapy, and is still receiving treatment for VIN 3.
- Case 4:** 30 yo F with MS on fingolimod since 10/2016 with HPV related cervical dysplasia. History includes normal pap testing with unknown HPV status followed by abnormal pap testing in 2017 showing LSIL. Patient required colposcopy and biopsy results are pending.
- Case 5:** 32yo F w/ MS on fingolimod since 2015 with HPV-related cervical dysplasia. History includes a HPV+ pap from 2011 to 2013. She then had normal pap results from 2015 through 2016. In 2017 pap results showed HPV+ and LSIL/CIN1.

Demographics

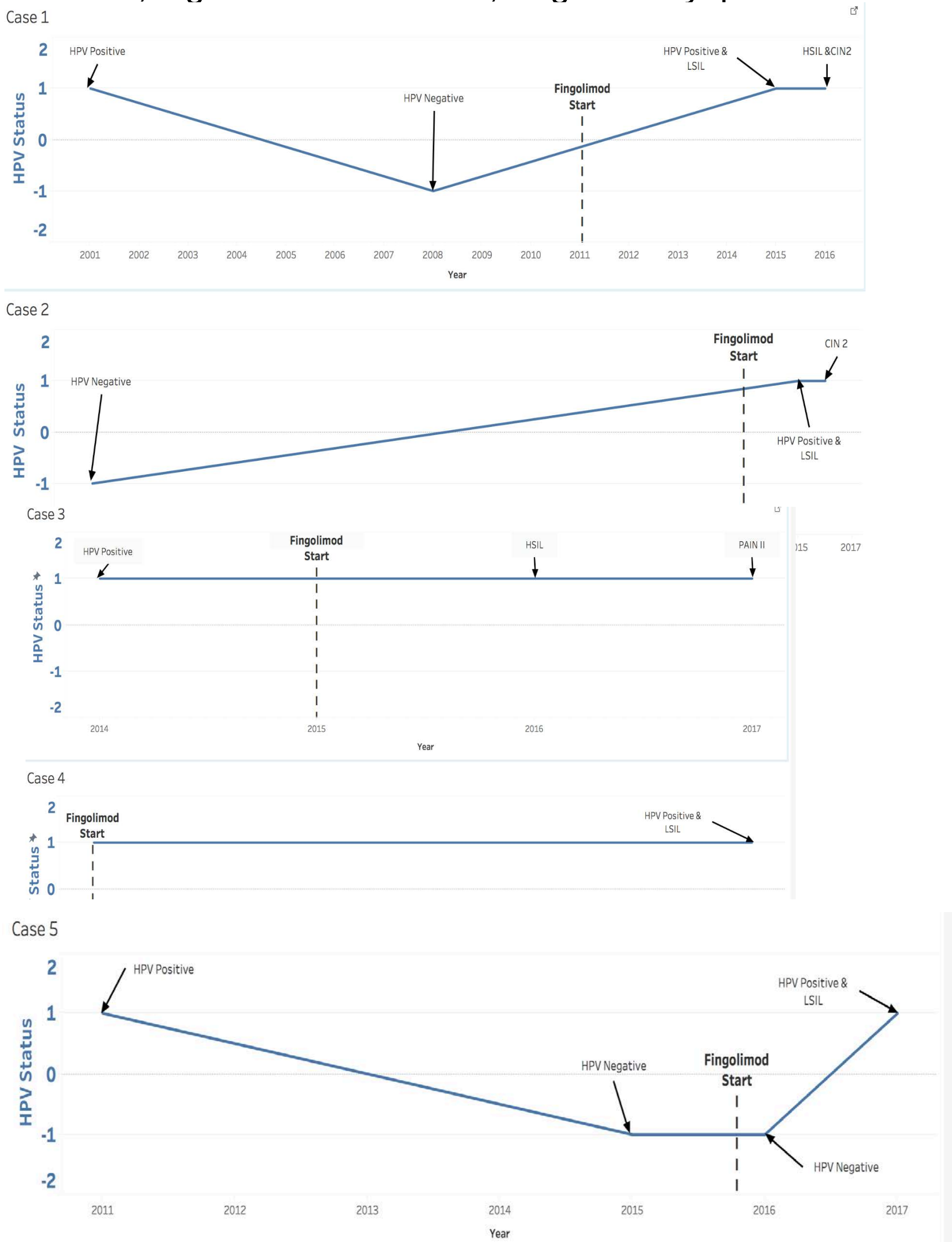
Age, Sex	Smoking history	Prior DMT use	Other concurrent immuno-suppressant therapy	HPV vaccination	# of sexual partners in the past 5 years	HIV status	Other autoimmune disorders
57 yo F	Former smoker	Copaxone, Rebif, Novantrone, Tysabri, LDN	None	No	1	Negative	None
45 yo F	Never	None	None	No	2	Negative	None
28 yo F	Never	None	None	Yes	1	Negative	None
30 yo F	Never	Avonex, Tecfidera.	none	No	Unknown	Negative	None
32 yo F	Former smoker	Copaxone	None	No	Unknown	Negative	None

Conclusions

There is a potential relationship between the use of fingolimod in women and the development of HPV-related cervical or other anogenital dysplasia.

Discussion

- Obtain HPV vaccination history and vaccinate according to guidelines as appropriate prior to initiating fingolimod.
- Obtain history of HPV status and consider performing gynecological exam with pap testing prior to starting fingolimod.
- Consider increasing the recommended frequency of surveillance exams for women testing positive for HPV.
- Further research is needed to determine if discontinuation of fingolimod is appropriate in individuals with HPV, high-risk HPV strains, or genital dysplasia or cancer due to HPV.



References

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