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 95% 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.
• Human papillomavirus (HPV) infections are responsible for approximately 90% of cervical cancers and other HPV-related anogenital cancers.
• 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.

Methods
• A retrospective chart review of five women with MS treated with fingolimod and known HPV with varying degrees of cervical or vulvar dysplasia.
• A 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 at 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 HSIL/VYN 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 2010 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 an 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

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Smoking history</th>
<th>Prior DMT use</th>
<th>Other concurrent autoimmune disease</th>
<th>HPV vaccination</th>
<th># of sexual partners in the past 5 years</th>
<th>HIV status</th>
<th>Other autoimmune disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 yo F</td>
<td>Former smoker</td>
<td>Copaxone, Rebif, Novantrone, Tysabri, LDN</td>
<td>None</td>
<td>No</td>
<td>1</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>45 yo F</td>
<td>Never</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>2</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>28 yo F</td>
<td>Never</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>1</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>30 yo F</td>
<td>Never</td>
<td>Avonex, Tecfidera</td>
<td>None</td>
<td>Unknown</td>
<td>Negative</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>32 yo F</td>
<td>Former smoker</td>
<td>Copaxone</td>
<td>None</td>
<td>Unknown</td>
<td>Negative</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

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
- 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 at 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.
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Addressing the challenges of HPV vaccinations

Neurology, 2, 174-81.

http://www.acog.org/Womenshealth/Human-Papillomavirus#HPV_15, 373-381.