Table. Correlates of Lack of Knowledge of Type of Skin Cancer Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Lack of Knowledge of Type of Skin Cancer Diagnosis</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Participants, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full sample</td>
<td>19.0 (16.4-21.6)</td>
<td>NA (NA)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Female 19.1 (15.6-22.6)</td>
<td>0.89</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male 18.8 (15.3-22.3)</td>
<td>0.98</td>
<td>(0.72-1.34)</td>
</tr>
<tr>
<td>Current age, y</td>
<td>18-49 17.2 (10.5-23.9)</td>
<td>1 [Reference]</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50-59 13.4 (8.2-18.6)</td>
<td>0.75 (0.39-1.43)</td>
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</tr>
<tr>
<td></td>
<td>60-69 19.1 (13.9-24.2)</td>
<td>1.13 (0.62-2.08)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>70-79 19.4 (14.1-24.4)</td>
<td>1.16 (0.65-2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≧80 26.4 (19.5-33.4)</td>
<td>1.73 (0.96-3.11)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Years since skin cancer diagnosis</td>
<td>0-5 19.2 (15.2-23.2)</td>
<td>1 [Reference]</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-10 18.6 (13.2-24.0)</td>
<td>0.96 (0.61-1.51)</td>
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</tr>
<tr>
<td></td>
<td>11-20 17.5 (11.9-23.1)</td>
<td>0.89 (0.56-1.42)</td>
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<tr>
<td></td>
<td>≧20 20.3 (13.1-27.5)</td>
<td>1.07 (0.65-1.77)</td>
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<tr>
<td>Education level</td>
<td>Some high school or less 29.4 (20.2-38.5)</td>
<td>2.50 (1.44-4.32)</td>
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<tr>
<td></td>
<td>High school graduate 21.8 (16.8-26.8)</td>
<td>1.68 (1.07-2.62)</td>
<td></td>
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<tr>
<td></td>
<td>Some college 18.2 (13.3-23.0)</td>
<td>1.33 (0.84-2.12)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>College graduate 14.3 (10.3-18.3)</td>
<td>1 [Reference]</td>
<td>0.001</td>
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</tr>
<tr>
<td>Annual family income, $</td>
<td>&lt;35 000 26.4 (21.4-31.4)</td>
<td>2.31 (1.34-3.98)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>35 000-74 999 18.5 (13.5-23.3)</td>
<td>1.46 (0.80-2.67)</td>
<td></td>
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<tr>
<td></td>
<td>75 000-99 999 8.1 (3.8-12.3)</td>
<td>0.56 (0.27-1.17)</td>
<td></td>
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<tr>
<td></td>
<td>≧100 000 13.4 (7.9-19.0)</td>
<td>1 [Reference]</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Self-reported health</td>
<td>Poor/fair 25.5 (18.7-32.3)</td>
<td>2.27 (1.40-3.69)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Good 21.8 (16.8-26.7)</td>
<td>1.84 (1.13-3.02)</td>
<td></td>
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<tr>
<td></td>
<td>Very good 16.6 (12.0-21.2)</td>
<td>1.32 (0.81-2.16)</td>
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<tr>
<td></td>
<td>Excellent 13.1 (8.7-17.5)</td>
<td>1 [Reference]</td>
<td>0.001</td>
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<tr>
<td>Health care coverage</td>
<td>Private 16.8 (13.8-19.8)</td>
<td>1 [Reference]</td>
<td>0.02</td>
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<tr>
<td></td>
<td>Public 22.9 (17.5-28.3)</td>
<td>1.48 (1.01-2.15)</td>
<td></td>
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<tr>
<td></td>
<td>None 32.2 (25.7-39.7)</td>
<td>2.46 (1.09-5.58)</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio. The data are from the 2007 and 2008 US National Health Interview Surveys (NHIS) conducted by the National Center for Health Statistics; sample sizes vary from n=1069 to n=1172. All percentages are weighted. Wald χ² test of association between the variable and lack of knowledge of type of skin cancer diagnosis.

T acrolimus ointment is an effective and safe treatment for moderate and severe atopic dermatitis (AD). The most common adverse event related to topical tacrolimus treatment is skin burning, which during the first week occurs in about every second adult and every third pediatric patient.1,2 The grade of irritation seems to depend on disease severity and erythema, and irritation usually decreases or stops within a week. In some patients though, the skin irritation is severe and long-lasting and prevents the use of tacrolimus ointment. Topical tacrolimus treatment can also cause an alcohol reaction after intake of even a small amount of alcohol. This reaction resembles the burning sensation at the beginning of the treatment. Acetylsalicylic acid (hereinafter, “aspirin”) seems to prevent the alcohol reaction caused by topical tacrolimus treatment, but to our knowledge, there are no reports on the effect of aspirin on the initial burning reaction.

Methods. This retrospective study was approved by the ethics committee of the Helsinki University Central Hospital. We enrolled 6 patients, aged 20 to 50 years, who had stopped tacrolimus treatment at least 1 month earlier owing to severe burning during the first days of therapy. We then treated them at the outpatient clinic of our hospital with systemic aspirin followed by tacrolimus. All patients had eczema in the head and neck area and moderate to severe AD (according to the criteria of
Rajka and Langeland). None was allergic to aspirin or had any severe upper intestinal tract problems. No patients had applied tacrolimus ointment for at least 1 month before the study began. Demographic characteristics and recent AD medications for all patients are summarized in the Table.

Patients took 500 mg of aspirin orally 1 hour before applying tacrolimus ointment, 0.1%, to all affected areas. During a 1-hour follow-up interview, patients assessed skin burning as none, mild, moderate, or severe. We then contacted the patients the next day to collect information on any burning that occurred later during the first treatment day.

Results. All patients experienced significantly less burning of the skin after tacrolimus treatment with aspirin therapy. Three patients reported no burning, while 3 reported mild burning after treatment with aspirin and tacrolimus ointment. None of the patients experienced burning later during the day.

Comment. These preliminary findings suggest that oral aspirin is effective in preventing severe burning caused by tacrolimus ointment during the first treatment days. Double-blind studies with larger patient numbers are needed to confirm these results. Further studies should continue to identify the mediators involved in the burning event, which could lead to a full understanding of the cascade.

The exact mechanism behind the tacrolimus-induced burning is unknown, but evidence supports the role of prostaglandins and neuropeptides, such as substance P. Topical application of tacrolimus on murine skin led to an initial release of substance P and calcitonin gene-related peptide from primary afferent nerve fibers during the early inflammatory response. In an in vitro porcine model, tacrolimus, similar to capsaicin, induced a transient increase in substance P release through activation of the transient receptor potential sub-type vanilloid-1 (TRPV1). The burning sensation caused by topical tacrolimus resembles that caused by topical capsaicin. Capsaicin-induced pain sensation and secondary hyperalgesia in humans can be reduced by topical aspirin treatment. Aspirin seems to have a direct inhibitory effect on the TRPV1, and this effect, together with the inhibition of prostaglandin synthesis through inhibition of cyclo-oxygenase, could explain the inhibitory effect of aspirin on the burning sensation caused by tacrolimus treatment in this study.

Aspirin also inhibits alcohol-induced application site erythema and burning after topical immunomodulator use. Trevisani and colleagues have shown that ethanol potentiates the response of TRPV1 to capsaicin and heat and lowers the threshold for heat activation of TRPV1 from 42°C to 34°C. Since capsaicin and tacrolimus seem to have a similar effect on the TRPV1, this could explain the alcohol reaction commonly seen in patients treated with topical immunomodulators.

In our practice we commonly recommend aspirin treatment for 2 to 3 days at the beginning of tacrolimus regimen for patients with AD (without contraindications to aspirin) who have severe erythema or who previously experienced severe burning during the early stages of treatment with topical immunomodulators. Aspirin should not be used for this purpose in children.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mandelin, Remitz, and Reitamo. Acquisition of data: Reitamo. Analysis and interpretation of data: Mandelin and Reitamo. Drafting of manuscript: Mandelin. Critical revision of the manuscript for important intellectual content: Mandelin, Remitz, and Reitamo. Administrative, technical, and material support: Mandelin, Remitz, and Reitamo. Study supervision: Mandelin, Remitz, and Reitamo.

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COMMENTS AND OPINIONS

Inadequate Biopsy Technique and Specimen Size: An Alarming Trend That Compromises Patient Care and an Appeal to Our Clinical Colleagues

With changes in the delivery of health care in America looming, dermatologists may increase the number of patients they see per time unit and biopsies they perform in an attempt to balance declining reimbursement rates. In addition, roughly one-third of dermatologists employ physician extenders. While this is often done with the explanation of a shortage of dermatologists, it may be also motivated by the desire to increase revenues.

See Practice Gaps at the end of this article

In 2005, Fernandez et al documented a trend toward smaller skin biopsy specimens over a period of 15 years (1988 to 2003) and concluded that a “definitive diagnosis may become increasingly difficult as the size of the biopsy specimens continues to get smaller.” (p339) It is not only the size of the specimen but also the type of biopsy that affects the histopathologic interpretation. This was most recently documented in a study published in the March 2010 issue of the Archives of Dermatology, which implied that punch and shave biopsies of melanoma lesions led to a higher risk of histopathologic misdiagnosis.

The Figure depicts only 5 examples of too-small or inadequately sampled specimens, among them a curedet melanoma, a shave biopsy extending only into the midepidermis to rule out basal cell carcinoma, and a shave biopsy to rule out alopecia areata. Although these examples vary between different practices, many dermatologists and physician extenders submit these types of inadequate specimens for histopathologic diagnosis. The examples document a trend, already suspected to be influenced by pressure to see more patients, in which dermatologists choose faster biopsy techniques such as shave, curettage, or 2-mm punch biopsies. When Kopf and Popkin initially popularized the use of the shave biopsy technique in dermatology in 1974, they certainly did not have in mind shaved specimens that barely scratch the skin surface. While aesthetic outcomes may be used as an argument, economic forces may play a larger role in the biopsy technique chosen.

Furthermore, lack of appropriate supervision of physician extenders can affect the patient care they provide, including their choice of biopsy technique and consequent too-small skin specimens for a reliable histopathologic diagnosis. As pointed out in the editorial published simultaneously with the study by Ng et al, “biopsy technique, per se, does not increase disease-specific mortality,” but it certainly increases the risk of histopathologic misdiagnosis. The dermatologist’s duties can be delegated to physician assistants or nurse practitioners, but liability or responsibility cannot.

We have to critically ask ourselves the following questions: How much are we willing to compromise biopsy size? And are we—as clinicians—truly aware of what we submit to the dermatopathologist and what effect our biopsy technique has on patient care? Or, to pose it more pointedly, are we practicing medicine to the highest ethical standards, if we submit biopsy specimens inadequate for histopathologic diagnosis? With America’s health care system under critical review, we appeal to our clinical colleagues to seriously consider adequate sample size and biopsy technique to deliver the most accurate histopathologic diagnosis and result in the best patient care.

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Paula Nelson, MD
Wilma F. Bergfeld, MD

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