and dysgeusia than the continuous regimen. Similarly, the muscle cramps and dysgeusia in the present patients resolved within 1 month after interrupting the vismodegib regimen.

Although pharmacokinetic studies have shown suboptimal efficacy and similar incidence and severity of adverse effects when vismodegib, 150 mg, was used once weekly or 3 times weekly, no studies to our knowledge have investigated the efficacy of continuous daily doses with drug breaks in between.  

We found a mean of 1.4 new surgically eligible BCCs per year per patient undergoing intermittent therapy, which is comparable to the 2.0 new surgically eligible BCCs per year per patient found by Tang et al in patients undergoing a standard continuous daily regimen.

Vismodegib resistance occurs in patients who undergo continuous vismodegib dosing.  

The frequency of resistance in patients who undergo an intermittent form of treatment is largely unknown. Combination therapy with hedgehog pathway inhibitors downstream of smoothened, such as itraconazole and arsenic trioxide, provide opportunities to increase efficacy and possibly reduce the incidence of resistance.  

Conclusions | Overall, our clinical experience suggests that intermittent therapy is an effective way to overcome problems with adverse effects and compliance with vismodegib treatment of BCNS. Photographic and histologic documentations of tumors and randomized clinical trials are warranted to quantify the ideal duration of the intermittent regimen and compare the addition of combination therapies to overcome potential drug resistance.

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Bullous Pemphigoid Associated With Linagliptin Treatment

Drug-induced bullous pemphigoid (BP) has been recently reported in association with sitagliptin and vildagliptin, 2 dipeptidyl peptidase-4 (DPP-4) inhibitors used in the treatment of type 2 diabetes mellitus (T2DM). Herein, we report the development of BP in 2 patients with T2DM treated with linagliptin, another DPP-4 inhibitor.

Report of Cases | Case 1. A man in his 60s with psoriasis and T2DM presented with pruritus and erythematous tense bullae on the limbs (Figure 1). The clinical diagnosis of BP was confirmed by histologic findings showing a subepidermal blister containing eosinophils (Figure 2) and direct immunofluorescence analysis showing a linear deposit of IgG and C3 at the basement membrane zone. Enzyme-linked immunosorbent assay was performed and demonstrated reactivity with the recombinant proteins of NC16a and C-terminal domains of BP180. Treatment with topical clobetasol propionate, 0.05% (50 g/d), improved the lesions, but the patient presented with another flare of BP 2 weeks later. Linagliptin treatment, which had begun 4 months previously, was stopped. One week later, under treatment with the same topical corticosteroid applications, the lesions healed completely; there was no clinical recurrence of BP during 3 months of follow-up.

Case 2. A woman in her 70s with T2DM presented with a 2-month history of pruritus and tense bullae on the trunk. The diagnosis

<table>
<thead>
<tr>
<th>IVT Regimen</th>
<th>Dermatologic Follow-up</th>
<th>Treatments Before IVT</th>
<th>Biopsy-Detected BCCs, No./y</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Every 6 weeks</td>
<td>Curettage and electrodesication, Mohs surgery</td>
<td>12 11 15 9 2 1</td>
<td>Muscle cramps, dysgeusia</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Every 3 months</td>
<td>Imiquimod, surgical excision, Mohs surgery</td>
<td>4 1 4 5 1 NA</td>
<td>Dysgeusia, muscle cramp, diffuse alopecia</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, surgically eligible basal cell carcinoma; IVT, intermittent vismodegib therapy; NA, not applicable; VT, vismodegib therapy.
of BP was confirmed by histologic and direct immunofluorescence analysis. Linagliptin treatment, which had been started 3 months previously, was stopped, and treatment with topical clo- betasol propionate, 0.05% (40 g/d), was started, with disappearance of all bullae within 5 days of treatment. Follow-up visits up to 5 months later revealed no clinical recurrence of BP.

Discussion | Both patients presented with an acute bullous eruption a few months after adding linagliptin to their treatment regimens. The clinical, histopathologic, and direct immunofluorescence features fulfilled the criteria of BP. Sustained remission was only achieved after definitive withdrawal of linagliptin therapy. The DPP-4 inhibitors are incretin-based treatments of T2DM that have been reported to induce BP. Ten cases of vildagliptin-induced BP and 4 cases of sitagliptin-induced BP have been reported to date1-3; 1 case occurred in a patient with psoriasis.2 To our knowledge, no case of linagliptin-induced BP was reported before the present observation.

The mechanism by which drugs can provoke BP is unclear. The DPP-4 inhibitors may induce anti-basement membrane zone antibodies or other structurally close antibodies, leading to subepidermal bullae and BP. Inhibition of DPP-4 has been shown to enhance the recruitment of eosinophils into the dermis,4 which may contribute to the blister formation and tissue damage observed in BP. The direct effect of gliptins on the BP180 antigen, the core target antigen in BP, has not been elucidated to date. However, in the skin, many cell types including keratinocytes constitutionally express DPP-4; the inhibition of DPP-4 might affect the epidermal basement membrane zone.5

In contrast to previously reported cases, neither of the present patients was undergoing metformin treatment, which makes this drug unlikely to be involved in the genesis of BP. In fact, metformin monotherapy has not been associated with BP1-3.

In addition, DPP-4 is known to be upregulated in keratinocytes in psoriatic lesions.6 The presence of psoriasis in our first case might have led to upregulation of DPP-4 in keratinocytes, thus potentiating the activity of gliptins on keratinocytes and modifying the immune response and/or altering the antigenic properties of the basement membrane and increasing the risk BP induced by DPP-4 inhibitors.

Our cases and the findings from the literature review demonstrate that BP is an adverse effect most probably shared by all types of gliptins. In view of their wide use in the treatment of T2DM, further studies are needed to determine the exact relationship between DPP-4 inhibitors, BP, and psoriasis.

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Primary Melanoma of the Penis in 3 Patients With Lichen Sclerosis

Genital lichen sclerosus (GLSc) is associated with squamous cell carcinoma (SCC), although the precise cause is not known. We describe 3 male patients with GLSc and primary penile melanoma. To our knowledge, a possible association between lichen sclerous and primary penile melanoma has not previously been discussed.

Report of Cases | Case 1. A man in his 50s presented with a firm nodule growing in the left coronal sulcus over 4 months (Figure). Three years earlier, he had been diagnosed with GLSc and unsuccessfully treated with topical steroid preparations of various potencies. Ultimately, he underwent a curative circumcision. The foreskin histologic analysis demonstrated GLSc. At last follow-up, he remained alive and well.

Case 2. A man in his 30s presented with a 1-year history of a slowly growing pigmented lesion on the glans of the penis. Clinically, melanoma was suspected, but he also had signs of active GLSc (a tight, scarred frenulum and a constrictive postthitis). An excisional biopsy showed a narrowly excised early radial growth phase mucosal lentiginous melanoma, Breslow thickness of 0.1 mm. He underwent wider excisional surgery and was also circumcised. The foreskin histologic analysis showed a primary nodular melanoma with a Breslow thickness of 0.44 mm. The melanoma was completely excised, and a circumcision was performed. At last follow-up, the patient remained alive and well.

Case 3. A man in his 40s presented with a pigmented macule of the glans penis of uncertain provenance. He had white sclerotic lesions of the glans and foreskin, biopsy of which confirmed GLSc. Histologic analysis of specimens from the pigmented lesion showed early radial growth phase melanoma with a Breslow thickness of 0.44 mm. The melanoma was completely excised, and a circumcision was performed. At last follow-up, the patient remained alive and well.

Discussion | Male GLSc is a lymphocyte-mediated dermatosis of controversial pathogenesis, but the weight of evidence points to chronic occluded exposure of a susceptible epithelium to urine. It is thought that chronic inflammation and scarring due to GLSc are the drivers to SCC. The published rates of this complication range from 0% to 12.5%.

Squamous cell carcinomas constitute 95% of penile cancers. Penile melanoma is responsible for less than 1% and typically occurs in the sixth and seventh decades of life; 50% occurs on the glans. It has an extremely poor prognosis (5-year survival, 31%). Although UV radiation is important in the pathogenesis of cutaneous melanoma, the cause of genital mucosal disease is obscure.

Primary vulval melanoma has been reported in women with coexisting GLSc. A possible causal relationship has been discussed, involving a pro-oxidative environment that increases the risk of mutations and disruptions of local mechanisms protecting against “melanocyte carcinogen.” However, the investigators note that the finding may be coincidental rather than causal.

To our knowledge, no cases of concomitant penile melanoma and GLSc have previously been reported. The occurrence of melanoma and GLSc observed in the 3 patients we describe herein may be a coincidence, but in 22 years of providing a dedicated genital dermatology service, these are the only penile melanomas that we have seen. In other words, no penile melanomas have been seen in the absence of GLSc.

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