Morphea-like skin reactions in patients treated with the cathepsin K inhibitor balicatib

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Background: In a multicenter clinical trial in North America and Europe that tested the cathepsin K (catK) inhibitor balicatib for the treatment of osteoporosis, several patients developed hardening of the skin.

Objective: We sought to characterize these observed adverse events.

Methods: Patients with skin hardening were examined by a local dermatologist. All of those patients except one had at least one biopsy specimen taken from affected skin, which was read by local and two central dermatopathologists. Workup was directed for consideration of systemic scleroderma.

Results: Nine patients of 709 treated with balicatib developed skin hardening and were given a diagnosis of morphea-like skin changes. No such events were observed in patients taking placebo or the lowest balicatib dose. After discontinuation of balicatib, skin changes resolved completely in 8 and partially in one patient.

Limitations: Each patient was seen by a different dermatologist in 6 different countries.

Conclusions: These observations are likely dose-related adverse effects of balicatib. Although catK was originally thought to be expressed only in osteoclasts, it has more recently also been found in lung and dermal fibroblasts and been implicated in the degradation of the extracellular matrix in the lung and the skin. It is therefore plausible that the observed dermal fibrosis in balicatib-treated patients is a result of impaired degradation of extracellular matrix proteins and may represent a class effect of catK inhibitors. We recommend that further exploration of catK inhibition for the treatment of osteoporosis or cancer should include monitoring for similar adverse effects. (J Am Acad Dermatol 2012;66:e89-96.)

Key words: balicatib; cathepsin K; collagen degradation; drug-induced morphea; osteoporosis treatment; scleroderma.
Cathepsin K (catK), a member of the cysteine protease family with strong collagenolytic and elastolytic activities, is highly expressed in osteoclasts, where it mediates bone resorption,\textsuperscript{1-8} and has been considered an attractive pharmacologic target to inhibit bone degradation, eg, for the treatment of osteoporosis.\textsuperscript{8-11} Four different daily doses (5, 10, 25, and 50 mg) of balicatib, a specific inhibitor of catK, were used in a 1-year, multicenter, double-blind, randomized placebo-controlled, safety and efficacy study in postmenopausal women with osteopenia/osteoporosis. In an extension study, patients on the 3 lower doses of balicatib were switched to 50 mg of balicatib for an additional 6 months. Here we report the observation of morphea-like skin changes in 8 of 541 patients treated with the catK inhibitor balicatib in that study (Fig 1) and in one patient treated with balicatib in an osteoarthritis study (55, 55, and 58 patients on 10, 25, and 50 mg; 55 on placebo). Because of these skin reactions, both studies were discontinued.

**CASE REPORTS**

Skin hardening affected mostly the trunk and the neck, except for patient 9, and was observed after 6 to 15 months (median 9 months) of balicatib treatment. The clinical characteristics, time course, and results of workup of affected patients are summarized in Table 1. No such skin changes were observed in any patient in the placebo group (n = 134) or in the group receiving the lowest dose of balicatib (5 mg; n = 134). All patients were evaluated and given a diagnosis by a local dermatologist. After discontinuation, skin hardening completely resolved in 8 patients within 5 to 31 months. In one patient, only partial resolution was observed 29 months after discontinuation.

Skin biopsy specimens were taken from 8 patients. All showed histologic changes typical for morphea or were considered consistent with morphea. There was no excessive deposition of mucin. Histologic findings of patients 2, 3, 4, and 9 are shown in Fig 2.

A biopsy specimen from an area between hardened skin and the surrounding erythematous ring on the right side of the chest of patient 1 (Fig 1, A) showed flattening of the rete ridges and a moderately dense perivascular, largely lymphocytic infiltrate with few eosinophils and plasma cells at the dermo-subcutaneous junction. The dermal thickness was uneven and therefore not unambiguously increased. Collagen fibers in the reticular dermis were slightly thickened. These findings were considered to be consistent with early inflammatory morphea.

Patient 5 denied a biopsy of skin changes, a mildly pruritic erythema around the front base of her neck and hardening with smooth and shiny skin surface on her breasts (Fig 1, D) and upper aspect of her back. The erythema was not pre-existent and the patient reported no significant prior sun exposure to this area. The skin firmness was measured using a durometer and found to be more than twice as high on the right breast (measured 5 cm from the mamilla: reading of 32) as on the nonaffected abdomen (measured 2 and 4 cm from the umbilicus: readings of 13 and 15, respectively). In the experience of the local dermatologist, skin firmness readings with this durometer usually do not differ significantly in these two areas.

Two biopsy specimens were taken from mildly pruritic, hardened, nonerythematous skin, one from the neck, and one from the abdomen of patient 6. None of these biopsy specimens showed the full thickness of the dermis or any adipose tissue and they were considered too small for a full evaluation. Nevertheless, there appeared to be thickened collagen bundles and a hypocellular and hypovascular dermis with loss of skin appendages. There was also a sparse inflammatory infiltrate of rare small lymphocytes. Direct immunofluorescence studies revealed negative findings.

Five months after skin hardening was first observed, a biopsy specimen was taken from a hardened, nonerythematous area on the abdomen of patient 7. It showed mildly swollen collagen bundles consistent with fibrosis. There was only sparse adipose tissue so that the overall thickness of the dermis

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**CAPSULE SUMMARY**

- Nine patients treated with the cathepsin K inhibitor balicatib developed dose-related morphea-like skin changes.
- As cathepsin K has recently been found to be expressed in dermal fibroblasts and to mediate degradation of collagen after its internalization into lysosomes, it is possible that the observation of dermal fibrosis represents a class effect of cathepsin K inhibitors.
- This may link this observation of drug-induced morphea-like skin changes to a specific pharmacologic mechanism.

**Abbreviations used:**
- ANA: antinuclear antibody
- catK: cathepsin K
- ECM: extracellular matrix
could not be evaluated. There was a moderate pandermal, mostly lymphocytic infiltrate with few plasma cells, mostly perivascular, but also around eccrine glands.

Patient 8 has been described previously. A biopsy specimen from the most hardened area on the left breast showed thickened and condensed collagen bundles in the reticular dermis and in thickened subcutaneous septae, with a mixed perivascular and periappendageal leukocytic infiltrate throughout the dermis and in the subcutaneous fibrotic strands, consisting of lymphocytes, monocytes, few eosinophils, and extremely abundant, cytologically normal-appearing plasma cells.
Table I. Findings in patients who developed morphea-like skin eruptions while taking balicatib

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Location</th>
<th>Age at trial entry, y</th>
<th>Medical and surgical history</th>
<th>Daily dose of balicatib, mg</th>
<th>Time in study until skin hardening, mo</th>
<th>Involved areas of skin hardening</th>
<th>Time until complete resolution of skin hardening after discontinuation of balicatib, mo</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Canada</td>
<td>67</td>
<td>—</td>
<td>50</td>
<td>9</td>
<td>Chest, abdomen (Fig 1, A)</td>
<td>9</td>
<td>SPEP, PFT, and high-resolution lung CT wnl</td>
</tr>
<tr>
<td>2</td>
<td>France</td>
<td>63</td>
<td>—</td>
<td>10</td>
<td>9</td>
<td>Chest, abdomen, axillae (Fig 2, A and B)</td>
<td>9</td>
<td>Low-titer antismooth muscle AB (1:50, normal &lt;20, no AB against SSA, SSB, or Borrelia; SPEP, PFT, high-resolution lung CT all wnl</td>
</tr>
<tr>
<td>3</td>
<td>Spain</td>
<td>61</td>
<td>HTN, hysterectomy</td>
<td>25</td>
<td>10.5</td>
<td>Chest, abdomen (Fig 1, B; Fig 2, C and D)</td>
<td>6</td>
<td>Monoclonal gammopathy (9.1%-10%) 4 mo before onset of skin symptoms (SPEP normal before and 3 y after discontinuation)</td>
</tr>
<tr>
<td>4</td>
<td>France</td>
<td>73</td>
<td>Hiatal hernia, lower back pain caused by degenerative arthritis (Forestier disease)</td>
<td>25/50</td>
<td>12 + 3*</td>
<td>Front of neck, mid to upper aspect of chest, upper aspect of abdomen, lower aspect of back (Fig 1, C; Fig 2, E and F)</td>
<td>31</td>
<td>Oligoclonal gammopathy (2 peaks, 25.2% and 3.6%) 6 mo after onset of skin symptoms, not seen 3 mo earlier, remained 9 mo after discontinuation, and resolved 2 y later; detection of IgM antiphospholipid AB (ELISA; 47 U/mL, normal 0-15 U/mL) and IgM antiphospholipid AB (67 IU, normal 0-15 IU) at time of skin fibrosis, not detectable after discontinuation of balicatib; ESR 58 mm/h no ANCA or ENA (Ro, La, SM, SM/RNP, SCL-70, histone); serology for Borrelia burgdorferi (IgG and IgM) negative, PFT and lung CT without evidence for restrictive lung disorder, normal esophagus manometry except slightly hypotonic inferior esophageal sphincter and waves (secondary to hiatal hernia), echocardiogram normal</td>
</tr>
<tr>
<td>5</td>
<td>Italy</td>
<td>64</td>
<td><em>Helicobacter pylori</em>-positive gastritis, breast implant (27 y earlier)</td>
<td>25</td>
<td>9</td>
<td>Neck, chest, upper aspect of back (Fig 1, D)</td>
<td>12</td>
<td>SPEP wnl; chest x-ray, lung CT, and PFT without evidence for fibrotic lung process</td>
</tr>
</tbody>
</table>

Continued
Table I. Cont’d

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Location</th>
<th>Age at trial entry, y</th>
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<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Poland</td>
<td>64</td>
<td>HTN</td>
<td>10</td>
<td>10</td>
<td>Neck, chest, abdomen</td>
<td>9</td>
<td>Monoclonal gammopathy 1 mo before onset of skin symptoms (0.42 g/dL, IgG κ; increasing to 0.76 g/dL 2 mo later), ESR 36 mm/h, slightly enlarged heart contour with widened aorta, but normal lungs in chest x-ray, ENA (SM, RNP, Ro, La, PM-ScI, ScI-70, Jo1) not detected</td>
</tr>
<tr>
<td>7</td>
<td>Poland</td>
<td>56</td>
<td>HTN, coronary artery disease, psoriasis</td>
<td>10/50</td>
<td>12 + 1*</td>
<td>Abdomen, breasts, side of neck</td>
<td>Only partial resolution after 29 mo</td>
<td>SPEP, chest x-ray, and PFT normal, high-resolution chest CT with impression of increased parenchymal density (but resolution problems of CT); ENA not detected, chest x-ray, lung CT, and PFT wnl</td>
</tr>
<tr>
<td>8</td>
<td>Italy</td>
<td>57</td>
<td>—</td>
<td>50</td>
<td>9</td>
<td>Chest, abdomen, buttocks, thighs, forearms</td>
<td>5</td>
<td>Monoclonal gammopathy (9.9%) 3 mo before onset of skin symptoms (not observed before and resolved 3 and 5 mo after discontinuation of balicatib)</td>
</tr>
<tr>
<td>9</td>
<td>Belgium</td>
<td>74</td>
<td>Hepatitis C, diabetes, breast reduction, vertical banded gastroplasty</td>
<td>25</td>
<td>6</td>
<td>Legs, forearms (Fig 2, G)</td>
<td>30</td>
<td>ANA 3+ positive with nucleolar pattern (at 1:40 dilution) at time of skin symptoms, 1+ positive 3 y after discontinuation of balicatib, ENA negative, SPEP and ESR wnl; PFT, high-resolution lung CT, and echocardiogram wnl</td>
</tr>
</tbody>
</table>

AB, Antibodies; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; ENA, extractable nuclear antibodies; ESR, erythrocyte sedimentation rate; HTN, hypertension; PFT, pulmonary function test; SPEP, serum protein electrophoresis; WNL, within normal limits.

*12 Months on lower dose of balicatib; additional months on 50 mg of balicatib.
Fig 2. Histologic changes of morphea-like skin changes in patients receiving balicatib. A and B, Patient 2: Biopsy specimen was taken from oval-shaped, ill-defined, firm, pearlescent plaques several centimeters in diameter surrounded by an erythematous ring on the abdomen of patient 2. Skin hardening was preceded by pruritic swelling in these areas. Biopsy specimen shows epidermis with effaced rete ridges, densely sclerotic, hypocellular and hypovascular dermis without appendageal structures, homogenized collagen bundles, and sparse perivascular lymphocytic inflammatory infiltrate in all layers of dermis. C and D, Patient 3: biopsy specimen was taken from an indurated area on medial aspect of left breast (Fig 1, B) 1 month after discontinuation of balicatib. At that time, skin hardening had already improved. It shows flattened epidermis with loss of rete ridges and densely sclerotic, hypocellular, hypovascular dermis without appendages. Collagen fibers are grouped in relatively large bundles. A bit of adipose tissue is found in one area at base of biopsy specimen, so that full thickness of the
A biopsy specimen from pruritic erythema on the thorax of patient 9 (who was enrolled it in the osteoarthritis trial) revealed a pandermal perivascular and interstitial lymphocytic infiltrate with scattered plasma cells, discrete interphase changes, and some loss of perieccrine adipocytes, but no homogenization of dermal collagen. These findings were considered consistent with early inflammatory morphea. Direct immunofluorescence studies produced negative results. The skin lesions resolved upon discontinuation of balicatib. However, 2 months later, the patient developed painful hardening of skin on both lower legs, extending to the forearms another 2 months later. A biopsy specimen from the forearms showed typical features of morphea (Fig 2, G). One year later, the pain improved, but the areas of skin induration expanded, now involving also the thighs. A biopsy specimen of the thighs then showed pandermal homogenization of dermal collagen and no inflammatory infiltrate.

Central laboratory investigations were done for all patients in the osteoporosis trial (including all of our patients, except patient 9), before the trial and in 3-month intervals during the trial, including serum protein electrophoresis, antinuclear antibodies (ANA), extractable nuclear antibodies, and immunoglobulins.

All patients with morphea were also evaluated by a local dermatologist. There was no sufficient evidence for systemic scleroderma in any of these patients; none developed Raynaud phenomena, difficulty swallowing, or microstomia. Swelling of the fingers with paraesthesia and slight sclerodactyly was observed only in one patient (No. 4). Before the trial, 4 patients had ANA ranging from 1:80 to 1:520, with speckled, nucleolar, or homogeneous pattern, but there was no significant titer increase during the trial for any patient. In one patient (No. 7), the ANA titer increased from 1:320 to 1:640 9 months after discontinuation of balicatib and to 1:1280 another 3 months later. Computer tomograms of the lungs were done in 6 patients and were all read by a central radiologist. One local reading reported increased parenchymal density, which was not confirmed by the central radiologist because of resolution problems. All of these 6 patients had normal pulmonary function test results.

Four patients received treatment, including methyldiphenisolone, methotrexate doxycycline, and hydroxychloroquine (patient 5), phototherapy (patient 6), cefuroxime (patient 7), or prednisone (patient 8).

DISCUSSION

Morphea (localized scleroderma) is a rare condition with a reported incidence rate of 12/1,000,000.13 We therefore consider the high rate of morphea-like skin changes (1:68 in the osteoporosis trial) to be a likely adverse effect of balicatib. All investigators of the clinical trial were informed of this adverse event after the first case of morphea had been reported. Nevertheless, the incidence rate may even be higher, as some skin changes, in particular subtle ones, may have remained underreported. Resolution in most patients after discontinuation of balicatib and the fact that these skin changes were most common with the highest dose and not observed with the lowest dose of balicatib suggest that these adverse events were dose related.

First evidence that catK’s collagenolytic activity is not limited to bone came from studies with catK knockout mice, which were shown not only to have a bone phenotype, but also to be more prone to develop bleomycin-induced lung fibrosis.14,15 More recently, catK has also been described to be strongly expressed in skin fibroblasts under certain conditions, including scars,16 and to mediate collagenolysis within lysosomes after endocytosis.17 This suggests that its extracellular matrix (ECM)-degrading properties may contribute to the maintenance of the homeostasis of the dermal ECM and counteract dermal fibrosing processes. Therefore, it is plausible that the observed skin fibrosis in the described patients was a result of the inhibition of dermis was probably represented, and considered increased. Few remaining blood vessels had perivascular lymphoid infiltrate containing few plasma cells and eosinophils in deep dermis and at the junction with subcutis. E and F, Patient 4: biopsy specimen from mid to upper aspect of chest (Fig 1, C) shows flattened epidermis with effaced rete ridges and densely sclerotic, hypovascular and hypocellular dermis with focally thickened collagen bundles and reduced number of appendageal structures. Fibrosis extends into subcutaneous septae. Eccrine glands are found not at the dermosubcutaneous junction, but higher in the dermis. Sparse perivascular infiltrate of lymphocytes, many plasma cells, and rare eosinophils seen throughout the dermis and at the junction with subcutis. G, Patient 9: biopsy specimen from forearms shows actinic elastosis, mild perivascular and periadnexal lymphocytic infiltrates, loss of perieccrine adipocytes, homogenization of dermal collagen, and thickening of the dermis.
matrix-degrading functions of catK in the skin. Skin fibrosing may therefore be a class effect of catK inhibitors. This would be in contrast to other drug- or toxin-induced sclerodermoid syndromes, in which primary pharmacologic or toxicologic molecular targets have not been identified.

Our observations also shed new light on the pathogenesis of morphea, as they suggest that failed ECM degradation (as opposed to, eg, increased ECM synthesis) may be a pivotal factor in this condition of pathological skin fibrosing.

In skin fibroblasts, catK mediates collagenolysis within lysosomes and not in the extracellular space, as it is not highly active or stable at neutral pH. Our observations strongly support a role of such intracellular degradation of ECM proteins, a so far largely underestimated pathway (as opposed to matrix metalloproteinase-mediated ECM degradation in the extracellular space).

Six of 8 biopsy specimens exhibited plasma cells in the dermal inflammatory infiltrates, which is also a common feature in spontaneous morphea. A monoclonal or biclonal gammopathy developed in 4 patients during balicatib treatment. The monoclonal peaks were noted either shortly before (3 patients) or soon after (one patient) the onset of skin hardening. These gammopathies resolved after discontinuation of balicatib in at least 3 patients. In the fourth patient, the further course is unknown. Although in both observations, the finding of plasma cells in the inflammatory infiltrates and the clonal gammopathies suggest activation of B cells, it remains unclear if these two are related. The fact that the patient with extremely abundant plasma cells (patient 8) also had a gammopathy would support such a relationship. It also remains unclear if the B-cell activation drives skin fibrosis in these cases, for example, by being directed against a particular cutaneous antigen. Direct immunofluorescence studies, which were done in two patients, did not reveal deposits of skin-reacting autoantibodies. An autoimmune pathogenesis has been suggested for spontaneous morphea, based on frequent observations of ANA and an association with other autoimmune conditions, but no significant changes of ANA titers were observed in our patients during the trial. Finally, it also remains unclear how inhibition of catK could predispose patients for such autoimmune reactions. The reported proinflammatory role of catK would rather suggest an antiautoimmune effect of catK inhibition, not a proautoimmune effect.

REFERENCES