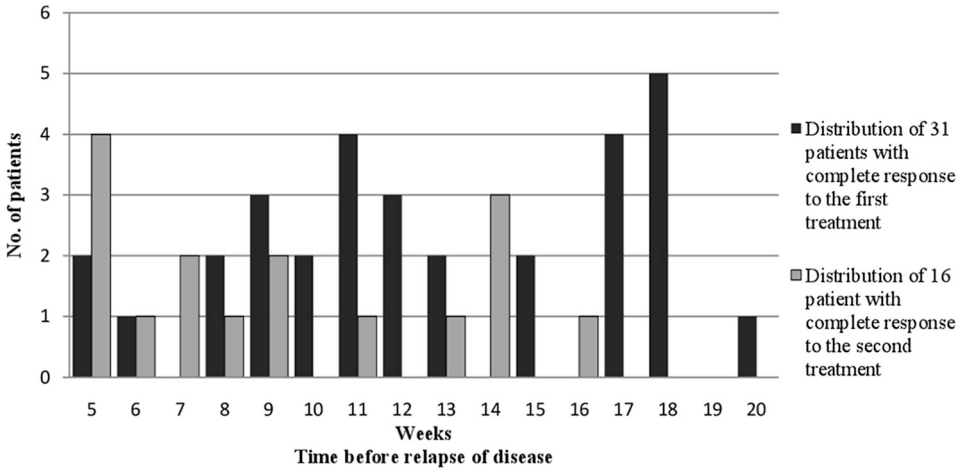

Fig 1. Distribution of occurrences of relapse of urticaria patients after first and second treatment with omalizumab. Patients who experienced relapse had an intensity of symptoms similar to the pretreatment period.

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Occurrence of vismodegib-induced cramps (muscular spasms) in the treatment of basal cell carcinoma: A prospective study in 30 patients

To the Editor: Vismodegib is a hedgehog pathway inhibitor approved for treating locally advanced and metastatic basal cell carcinoma. Cramps (muscular spasms) are among vismodegib's major adverse effects (40%-80% of patients).[1,2] In the pivotal study of Sekulic et al, 72.1% of treatment discontinuation occured within the first year of follow-up.[2] A recent study shows that stretching muscles before going to sleep reduces both the frequency and severity of nighttime cramps.[3] Our objective was to characterize cramps and discuss an appropriate treatment.

We assessed the occurrence and evolution of cramps in all patients treated with vismodegib at Lille University Hospital (Supplementary Appendix; available at http://www.jaad.org), in a prospective study conducted during September 2014-November 2015. Patients completed a questionnaire that was developed in collaboration with a specialist in neuromuscular diseases to determine the characteristics of patient muscle spasms. We evaluated the benefits of hydration and muscle stretching performed by physiotherapists or by patients themselves following guidelines from a recent study.[3]

Thirty patients were included in this study; 72% experienced muscle spasms, with 14% categorized as grade III according to Common Terminology Criteria

Table I. Comparison of muscle spasm characteristics

Characteristics	Present study	STEVIE 2015[1]	Sekulic 2012 and 2015[2]
Treatment dosage	150 mg daily	150 mg daily	150 mg daily
No. patients	30	499	96
Age, y	73.6	72	62
All grades, % (n)	72.4 (21/29*)	64	68
Time to onset, mo, median (range)	2.0 (0.69-6.87)	2.83 (2.30-3.68)	1.89 (1.35-2.73)
CTCAE grade I, % (n)	31.0 (9)	33	48
Time to onset grade I muscle spasms, mo, median (range)	2.27 (0.8-6.7)		
Time to onset (first muscle spasms), mo, median (range)	2.17 (0.9-6.9)		
CTCAE grade II, % (n)	27.6 (8)	23	16
Time to onset grade II muscle spasms, mo, median (range)	3.2 (0.9-6.5)		
Time to onset (first muscle spasms), mo, median (range)	2.27 (0.9-4.6)		
CTCAE grade III, % (n)	13.4 (4)	8	4
Time to onset grade III muscle spasms, mo, median (range)	4.14 (2.8-5.5)		
Time to onset (first muscle spasms), mo (range)	1.41 (0.8-2.8)		
Discontinuation, % (n or n/total)			
All patients	65.5 (19)	80 (400)	72.1 (75)
No muscle spasms	22 (2/9)		
With muscle spasms	81 (17/21)		
Grade I	78 (7/9)		
Grade II + III	83 (10/12)		
P value	.031		
Exposure to vismodegib, mo, median (range)	6.2 (0.59-10.97)	8.4	13.3, metastatic basal cell carcinoma cohort; 12.7, advanced basal cell carcinoma cohort
Discontinuation rate due to side effect, % (n/total or n)	63 (12/19)	36 (180)	17.3 (18)
Discontinuation rate due to muscle spasms, % (n/total or n)	31 (6/19)	9 (44)	

CTCAE, Common Terminology Criteria for Adverse Events.
*Data were missing for one patient.

for Adverse Events. The median duration (range) of treatment with vismodegib was 6.2 (0.59-10.97) months. Nineteen patients (65.5%) discontinued treatment during the year following the initiation. Seventeen of these 19 (89%) presented with muscle spasms; 12 patients stopped treatment because of adverse events and 6 because of cramps. We found a significant difference in vismodegib discontinuation ratios between patients with and without muscles spasms ($P = .0311$). Patients usually stopped treatment after 6 months because of good response or the occurrence of toxicity. Sekulic et al observed a lower discontinuation rate related to adverse events (17%), but 23% had stopped treatment following their own judgment.[2] Side effects could have been one of the reasons. In our study, muscle spasms appeared, on average, 2 months after treatment initiation. Patients with higher-grade muscle spasms had earlier and rapidly worsening symptoms (Table I; Supplementary Appendix).[1,2]

Among the 19 patients suffering from muscle spasms, 13 agreed to complete the questionnaire, and results were heterogeneous. Muscle spasms affected lower (92%) and upper (53.8%) limbs, occurred at night (84.6%), at rest (75%), and affected daily activities. Symptoms were described as painful peaks (84.6%). Thirty-eight percent suffered on a daily basis and 23.1% several times a week. (Table II).[4,5]

Eight patients with muscle spasms persisting for >1 month were prescribed stretching (Supplemental Fig 1, *A-C*; available at http://www.jaad.org) and hydration. Six of these patients (75%) improved; 5 patients had a grade decrease from II to I, and 1 patient expressed general improvement. Vismodegib was continued. No treatment (magnesium, baclofen, gabapentine, quinine benzoate) had a significant effect on muscle spasms. Patients in our cohort were mainly >60 years of age and on multiple medications. Managing cramps with stretching exercises without additional medications can help prevent other drug-induced toxicity and interactions in elderly patients.

Table II. Comparison of muscle spasm characteristics

Characteristics	Primary muscles cramps[4]	Statin-induced cramps[5]	Cramps related to vismodegib in Lille cohort
Age, y, average	All	58.7	72.4
Type of symptoms		Highly heterogeneous	Some similarities
Frequency of muscle cramps	Unknown	Low (could be underestimated); 1%-5% in controlled clinical trials; 29% in observational cohorts	70%
Musculoskeletal pain before treatment with statin/ vismodegib (%)		Common but usually different types of symptoms (84.1)	None
Elevation of CK level	No	Rare	1 patient
Time symptoms appeared	At night		84.62% at night; 30.7% in morning; 2% in afternoon
Time to onset		1 mo	2 mo
Affected muscles	Calf muscles; feet and root of lower limbs	Widespread; lower limbs (thighs, calves)	92.3% lower limbs; 53.8% upper limbs
Intensity	Unbearable		7.5 (VAS)
Triggering factor	Still underexplored, posture, exercise	41% yes; 53% unusual physical exertion; 30% taking new medication	Not found
Duration	Possibly several hours	Continuous intermittent pain	15-30 min 46%; <5 min 15%; continuous 9%
Frequency			38% daily basis; 23.1% several times a week; 15.4% 1X/week
Occurrence	During sleep	38% during daily activities	75% at rest
Impact on daily activities, %	Rarely affects daily activities	4	46
Associated pain	No	Tendonitis	No
Drug therapies efficiency	Unproven	Unproven	No improvement
Management of muscle symptoms	Stretching, quinine, anticonvulsant drugs, botulinic toxin, verapamil	Switching to a different statin, continuing statin at lower dosage	Stretching, treatment options under evaluation

CK, Creatine kinase; *VAS*, Visual Analog Scale.

Our prospective study shows that vismodegib-induced cramps might significantly hinder the treatment of basal cell carcinoma. Temporarily discontinuing vismodegib or offering physical therapy should be considered as complementary solutions.

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The multidisciplinary tumor board for the management of cutaneous neoplasms: A national survey of academic medical centers

To the Editor: The multidisciplinary tumor board (MTB) is a meeting of various medical specialties to discuss the management of patients with cancer. In lung, esophageal, and head and neck cancers, tumor boards increase adherence to national treatment guidelines, decrease treatment delays, are educational, and instill the importance of multidisciplinary care early in training.[1-4] However, little is known about the MTB for cutaneous neoplasms. This study assesses the structure, goals, and participation patterns of the MTB in a nationwide sample of academic dermatology centers.

Over 6 weeks, 3 requests to complete an online survey (Appendix 1 available at http://www.jaad.org) were emailed to all 119 dermatology residency programs accredited by the Accreditation Counsel of Graduate Medical Education as of January 5, 2016.[5] The results are presented in Table I. Fifty of 119

Table I. Tumor board characteristics

	No.	%
Total programs with a MTB	42	84.0
Single tumor board for all skin cancers?	23	54.8
Separate tumor boards for some skin cancers?	19	45.2
Which attending physicians are present at >50% MTBs?		
Dermatologic surgery	36	85.7
General dermatology	30	71.4
Surgical oncology	39	92.9
Medical oncology	39	92.9
Radiation oncology	35	83.3
Pathology	38	90.5
Plastic surgery	11	26.19
Otolaryngology	19	45.2
Diagnostic radiology	14	33.3
Other attendees at >50% MTBs?		
Community physicians	3	7.1
Residents/fellows	37	88.1
Medical students	18	42.9
Midlevel providers	20	47.6
Ancillary staff (eg, nurse/social worker)	18	42.9
Do community physicians present patients?		
Yes	6	14.3
Are dermatology residents required to attend?		
Yes	9	21.4
Do patients attend?		
Yes	4	9.5
Can physicians at your center participate via videoconference?		
Yes	11	26.2
Can outside physicians participate via videoconference?		
Yes	3	7.1
Would you participate in a multi-institution MTB via videoconference?		
Yes	24	57.1
Is there a notification process to inform patients they were discussed at a MTB?		
Yes	23	54.8
Are the reasons for case discussion shared before the MTB?		
Yes	25	59.5
Is there a listserv of MTB participants to allow for case discussion?		
Yes	7	16.7
No, but it would be useful	33	78.6
No, and it would NOT be useful	2	4.8
When do the meetings begin?		
Before 8 AM	16	38.1
8 AM-noon	6	14.3

Continued

SUPPLEMENTARY APPENDIX

Population of study

All patients were ≥18 years of age. All patients taking vismodegib in the Department of Dermatology of Lille Hospital were included. Diagnosis was confirmed by histologic examination. Patients were inoperable because of previous local treatment failure or extremely damaging treatment. Treatment with vismodegib was validated by a multidisciplinary team of plastic surgeons, dermatologists, radiotherapists, and medical oncologists. Patients with Gorlin syndrome were allowed to participate. Approval and waiver of informed consent in agreement with French regulations concerning such studies was obtained.

Treatment and follow-up

Vismodegib was prescribed at a standard dosage regimen of 150 mg daily. Follow-up was performed by a dermatologist each month. Side effects were graded using the Common Terminology Criteria for Adverse Events v4.0: grade I was mild pain, grade II was pain interfering with instrumental activities of daily life, and grade III was pain interfering with basic activities of daily life. Standard blood tests revealing magnesium and creatine kinase (CK) levels were performed at each visit. The efficiency of muscle spasm treatments (magnesium, quinine) and the efficiency of physiotherapy were measured by recording changes in cramp Common Terminology Criteria for Adverse Events grades and patients' general impressions.

Other results

No relationship between muscle spasms and high CK levels was identified. No variation in magnesium levels was observed in our patients. Four patients who were examined by a neurologist did not present with signs of neuropathy. We performed electromyograms on 2 patients with major muscle spasms and 1 patient with grade I muscle spasms. No sign of neuropathy was identified.

The literature

Similar side effects have been reported with sonidegib—another hedgehog pathway inhibitor—in 51.9% of patients treated with a 200-mg dose and in 69.3% of patients treated with a 800-mg dose, suggesting a class effect. Similarly to vismodegib cases, muscle spasms were the main reason for frequent discontinuation of sonidegib treatment.[S1] In other studies, magnesium therapy did not appear to be effective in the treatment of nighttime leg cramps either.[S2] Quinine (200-500 mg daily) does not seem to significantly reduce muscle spasms, and some countries have restricted its use because of the serious adverse effects it can cause.[S3]

SUPPLEMENTAL REFERENCES

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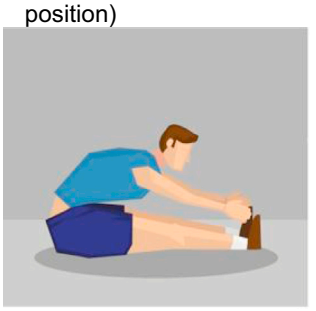
Stretch	Description
Calf stretch (standing position)  **A**	Starting position: Stand tall, with one leg in front of other, heels pressed onto ground, and hands pressed flat against wall at shoulder height. Stretching exercise: Fold the front leg's knee with the rear leg, keep spine straight and soles of feet in contact with floor at all times. The stretch should be felt in the calf of the rear leg. Hold for 10 seconds. Repeat with the other leg.
Hamstring stretch (standing position)  **B**	Starting position: Place one heel on a low stool or a box. Both front and rear legs should be stretched. Stretching exercise: Lean forward while keeping the back straight. The rear foot sole should be in contact with the ground at all times The stretch should be felt in the hamstring. Hold for 10 seconds. Repeat with the other leg.
Hamstring and calf stretch (sitting position)  **C**	Starting position : Sit on the ground with both legs straight out. Grab both feet with hands. Stretching exercise: Lean forward while keeping back straight. Stretch should be felt in both calves and hamstrings. Hold for 10 seconds.

Supplemental Fig 1. Descriptions of stretching exercises.