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Evolution of bone mineral density in patients treated with high-dose topical corticosteroids for a bullous pemphigoid

Nolwenn Ropars

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ANNEE 2016



THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
FACULTÉ DE MEDECINE
sous le sceau de l'Université Européenne de Bretagne

THÈSE EN VUE DU
DIPLÔME D'ÉTAT DE DOCTEUR EN MEDECINE

Présentée par

Nolwenn ROPARS

née le 25 janvier 1988 à Brest

**Evolution de la densité minérale
osseuse chez des patients traités
par dermocorticothérapie
prolongée pour une pemphigoïde.**

**Evolution of bone mineral density
in patients treated with high-dose
topical corticosteroids for a
bullous pemphigoid.**

**Thèse soutenue à RENNES
le 26/04/2016**

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ABSTRACT

Introduction: High dose topical corticosteroids may have same systemic side effects as systemic corticosteroids. Bone side effects are poorly known with topical corticosteroids. We studied evolution of Bone Mineral Density (BMD) in patients with Bullous Pemphigoid (BP) treated with high dose of clobetasol propionate in a retrospective monocentric cohort.

Material and Methods: BMD measurements and biological analysis were performed before and after topical corticosteroid treatment in patients with BP from January 2014 to June 2015. Tubes of clobetasol propionate were count every month. The objective was to describe changes in BMD and biological markers according to the dose of clobetasol propionate in patients with BP.

Results: 29 patients had BP, 22 patients had at least one assessment, and 9 patients had two assessments. 6 patients had a BMD variation > 0.03 g/cm². There was no correlation with dose of clobetasol propionate. There was no biological change before and after treatment. Limitations were missing data, small size of the sample, and number of patients excluded because high mortality of BP.

Conclusion: These results suggest larger studies to analyse links between high dose of topical corticosteroids and osteoporosis in patients with BP.

INTRODUCTION

In France, first-line treatment for Bullous Pemphigoid (BP), an auto-immune bullous dermatosis, currently lies on prolonged use of high dose superpotent topical corticosteroid (1).

Use systemic corticosteroids was considered the mainstay treatment for BP patients (2,3), until a large French multicenter prospective randomized trial (4) showed that clobetasol propionate cream was more effective than systemic corticosteroids in disease control on day 21, and presented with a lower rate of severe systemic side effects. Another French multicenter randomized prospective trial (5) compared two regimens of topical corticosteroids and showed that a shorter treatment (4 months vs 12 months) using lower doses of clobetasol propionate (10-30 gram (g) vs 40 g per day) was as effective as the standard regimen with fewer life-threatening side effects. Consequently, clobetasol propionate cream has become the BP treatment of reference in France.

Systemic absorption following cutaneous application of corticosteroid cream ranges between 0.05 % and 0.3 % (6) and may cause systemic side effects. Cases of iatrogenic Cushing (7), adrenal suppression (8–13) or hyperglycemia (14–16), have been reported following cutaneous application caused by improper and prolonged usage of super potent topical corticosteroid. These side effects are well described with systemic glucocorticoids. Few cases of topical corticosteroids-related bone side effects (17–22) have been reported. Osteoporosis is one of the most frequent and clinically relevant side effect of long-term systemic glucocorticoid therapy (23) and not described with topical corticosteroid. Osteoporosis is a disease characterized by a reduce in bone strength, leading to an increased risk of fracture and related increases in morbidity and mortality (24). Bone strength is estimated by measuring bone mineral density (BMD). Cross-sectional studies have evidenced low values for BMD in patients with atopic dermatitis (25,26) and psoriasis (22,27). However, low BMD may be due to absorption of topical corticosteroids or to chronic inflammation.

The aim of the present study was to evaluate the change of BMD during high dose topical corticosteroids treatment in patients with BP.

MATERIALS AND METHODS

We performed a retrospective monocentric review of newly diagnosed BP who attended the dermatological department in Rennes University Hospital from January 2014 to June 2015. For all BP patients, the diagnosis of active disease was established on the basis of the presence of blisters on the skin as well as the typical immunopathological criteria such as linear deposition of IgG and C3 at the basement membrane zone on direct immunofluorescence and circulating levels of anti BP180 and/or anti BP230 autoantibodies by ELISA.

Patients were treated with an initial dose of clobetasol propionate cream ranging from 20 to 40 g per day. The clobetasol propionate cream was tapered over 4 months according to the following protocol driven by SFD (Société Française de Dermatologie) guidelines: clobetasol propionate cream every day the first month, every other day the second month, twice a week the third month and once a week the fourth month. If there were less than ten blisters, the treatment was the same but with only 20 g per application. Osteoporosis prophylaxis was not routinely given.

In our Dermatology department, all newly BP underwent physical, biological examinations (complete blood cell counts, blood electrolyte, blood sugar, serum creatinine, thyroid stimulating hormone (TSH), parathyroid hormone (PTH), morning serum cortisol, electrophoresis, and markers of bone metabolism: serum calcium (adjusted with albumin), urinary calcium, serum phosphate, 25-hydroxyvitamin D (25-OHD), total alkaline phosphate, C-terminal telopeptid of type 1 collagen (CTx), N-terminal propeptide of type I procollagen (P1NP)) and a BMD measurement at the initial visit and after treatment (about 6 months later). Biological samples (blood electrolytes, blood sugar and creatinine) were performed every month.

Every month, at each follow up visit, the patients underwent physical examination and the number of new bullae that appeared daily was recorded, together with the number of empty tubes of clobetasol propionate that had been used. In this article, clobetasol propionate is expressed in grams: 10 g of clobetasol propionate correspond to one tube of topical corticosteroids containing 5 mg of clobetasol propionate.

BMD was measured in all patients at the lumbar spine, hip and femoral neck using Dual energy X-ray Absorptiometry (DXA)(Hologic QDR 4500 Bone Densitometer) in a single laboratory. The BMD are expressed in gram per square centimeter after which the Standard Derivation (SD) was calculated. Data was expressed as T-score (number of SDs from the mean value of the young adult of the same sex reference population). DXA was reported by one investigator who was aware of the patient's diagnosis but not of the frequency, amount or duration of clobetasol propionate used. We considered a meaningful BMD change above 0.03 g/cm² between both DXA at any site (28,29). Otherwise, bone density was considered stable. WHO Fracture Assessment Fracture tool (or Frax-tool) was calculated for all patients with necessary data according to recommendations (30) of the French Society of Rheumatology and the Groupe de Recherche et d'Information sur les Osteoporoses (we considered no familial history of osteoporosis).

Fracture risk factors were collected: history of osteoporosis with fracture, history of prolonged systemic corticosteroids, prolonged immobilization, current smoker, alcohol consumption, BMI < 19 kg/m². Parental hip fracture, calcium intake, ages and treatment of menopause could not be evaluated in this study. We retrospectively collected data from the medical records.

We compared change of BMD and blood analysis before and after the treatment with clobetasol propionate. The objective of this retrospective cohort was to describe changes in BMD and biological markers according to the dose of topical corticosteroids.

The statistical analysis was done with SAS software (version 9.4). Continuous variables were expressed by mean and standard deviation and categorical variables were expressed by the number of patients and percentages. Comparisons between M0 and M6 were realized using Wilcoxon signed rank test.

RESULTS

A total of 29 patients with BP attended the dermatological department of Rennes University Hospital between January 2014 and June 2015. Among the 29 patients, 22 had at least one BMD measurement and biological examination. Among them, 9 patients had 2 BMD measurements and biological examinations (flow chart **figure 1**).

Table 1 shows clinical and biological baseline characteristics of patients. All patients had more than 70 years. Eighteen of them had at least one additional risk factor of fracture. The median BMI was 26.7 ± 6.0 kg/m². Thirteen patients were bedridden. Five patients had history of osteoporosis with fracture. Among these 5 patients, 1 had bisphosphonate treatment, 1 had calcium plus vitamin D treatment and 3 had vitamin D treatment alone. There was no patient with rheumatoid arthritis or with secondary osteoporosis. Frax-tool was calculated for patients without systemic corticosteroids, but could be calculated for only ten of the nineteen patients. For the other patients femoral necks BMD, weights or heights were missing. Among the ten patients, only two patients had an indication of osteoporosis treatment.

Baseline BMD measurements are presented in **table 2**.

Among the 22 patients, 11 patients had baseline < 10 bullae per day. Thirteen patients could not be evaluated and 9 patients were evaluated after treatment. Mean cumulative dose of clobetasol propionate was 2070 ± 922 g. Five patients had an initial treatment with 30 g per day and 4 patients had 20 g per day. One patient (patient 1) was evaluating at 12 months. He was treated with a cumulate dose of 7220 g of clobetasol propionate. Six of the 9 patients with two assessments were in clinical remission at 6 months. Four patients still have clobetasol propionate treatment at 6 months. Three of these 4 patients had lower cortisol measurements after 6 months. Only patient 27 had a collapsed cortisol with no clinical symptom. He was treated with $2270 \text{ g} \pm 929$ g of clobetasol propionate. There was no fracture during or after treatment.

Nine patients had initial and final evaluations. There was no significant biological variation before and after treatment especially in blood sugar, serum calcium, urinary calcium, serum phosphate, 25-OHD, alkaline phosphate, CTx and P1NP for the nine patients with two assessments. **Figure 2** presents schematically all variations for the 3 sites measurements together with the cumulative dose of clobetasol propionate. Among the 9 patients with both an initial and final BMD evaluations, 6 had a bone density loss and 3 were stable, without bone density loss. The mean bone loss at 6 months was $- 5.0 \pm 6.4\%$ at the lumbar spine, $- 4.8 \pm 4.5\%$ at the hip and $- 4.6 \pm 7.5\%$ at the femoral neck. Clinical and biological characteristics of patients with or without bone density loss are compared in **table 3**. P1NP was higher with no significant difference between patients with and without bone loss. Calcium and 25-OHD were higher in patients with bone density loss compared to patients without. Paradoxically, the mean cumulative dose of clobetasol propionate per patient was lower in patients with bone density loss, compared to the patients without bone density loss, and no obvious correlation between clobetasol propionate dose and bone density variation was observed (**figure 3** for lumbar site measurements, and data not shown for other sites).

DISCUSSION

In our study, among 9 BP patients treated with high dose of superpotent topical corticosteroids, 6 had BMD loss. No obvious correlation with cumulative or daily dose of clobetasol propionate was observed.

BMD decrease with systemic corticosteroid has been well described (31,32). Significant decrease is observed within the first six months (5 to 15%) then 2% per year in lumbar spine and femoral neck (33). This BMD decrease depends on the daily dose (34) and duration of corticosteroid therapy, rather than the cumulative dose. BMD decline is reversible when corticosteroid treatment is stopped (35–37). Current recommendations for prevention treatment of osteoporosis are to treat patients according Frax-tool and to treat all patients over 70 years having systemic corticosteroids for more than 3 months (38).

In immunobullous disease, change of BMD with systemic corticosteroids was – 0,6% in lumbar spine and + 1% in femoral neck at six months in a prospective study (39) on 14 patients supplemented with calcium and vitamin D. An association between pemphigus and osteoporosis reported independently of corticosteroid use has been reported (40). Immunobullous disease by itself might be associated with bone fractures (41), although the respective roles of corticosteroid and low vitamin D level are not easily disentangled.

Examples of low BMD have already been reported to be associated with atopic dermatitis (25,26) and psoriasis (27), with difficulties in assessing the respective responsibilities of corticosteroids and chronic inflammation. Cases of femoral head necrosis (17–21) and bone fractures (22) in patients with no other risk factor than topical corticosteroids have also been reported. The role of topical corticosteroid remains unclear (42–47). Systemic absorption is as low as 0.05% to 0.3% (6) have been shown to lead to systemic side effects such as cushing, adrenal suppression or hyperglycemia. BP treatment in France may represent a specific situation because of the singularity of the therapeutic scheme with high dose of superpotent corticosteroid during 4 months (1).

In our study, 6 of the 9 patients with both BMD measurements had a BMD loss but relations with cumulative or daily dose of topical corticosteroid were unclear. Only one of the six patients had a collapsed cortisol. Diminution of cortisol during treatment with topical corticosteroids was already reported (8–13) especially with a dose of clobetasol propionate over 50 g per week (8) and return to normal after stopping treatment if less than 50 g per week is applied (8,48).

In our study, patients with BP had multiple risk factor of fracture, in addition to age. There was no obvious relationship between BMD change and baseline BMD status, or risk factors for osteoporosis. Even if no significant variation were found between both groups, patients with higher dose of P1NP had a BMD change. There were more at risk of osteoporosis due to a high bone turnover, according to other study (49,50).

In our study a high mortality rate was observed. The relevance of implementing a systematic prevention of osteoporosis in BP patients is questionable because of the high mortality rate in older BP patients (51–53).

Our study has several limitations. First because of the retrospective nature of the study, data missing partly hampered the analysis. However, the amount of clobetasol propionate was precisely collected and was available for all the 9 patients with both BMD measurements. Second, our sample size was small, and made smaller by a high attrition rate in a population with a high mortality rate; the sample size was large enough, however, to evidence a decrease in BMD in 6 of the 9 patients, and we were able to describe the bone status in 22 patients with BP. Last, we had no information on the pre-treatment dynamics of bone loss in our patients, this piece of information would have been of great value to fully interpret the specific role of dermocorticosteroid in BMD decrease, by allowing a comparison between the periods before and during dermocorticosteroid therapy.

CONCLUSION

Our results suggest that larger studies would be interesting to analyze the links between high dose of clobetasol propionate and osteoporosis in patients with bullous pemphigoid. It seems necessary to continue systematic evaluation of risk factor of osteoporosis for patients with bullous pemphigoid and to propose prevention on case-by-case basis.

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Evolution de la densité minérale osseuse chez des patients traités par dermocorticothérapie prolongée pour une pemphigoïde.

Rennes, le 03/03/16

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G. CATHELINEAU

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GLOSSAIRE

BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Bullous Pemphigoid
CTx	C-terminal telopeptid of type I collagen
DXA	Dual energy X-ray Absorptiometry
P1NP	N-terminal propeptide of type I procollagen
PTH	Parathyroid hormone
SD	Standard Derivation
SFD	Société Française de Dermatologie
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization
25-OHD	25-hydroxyvitamin D

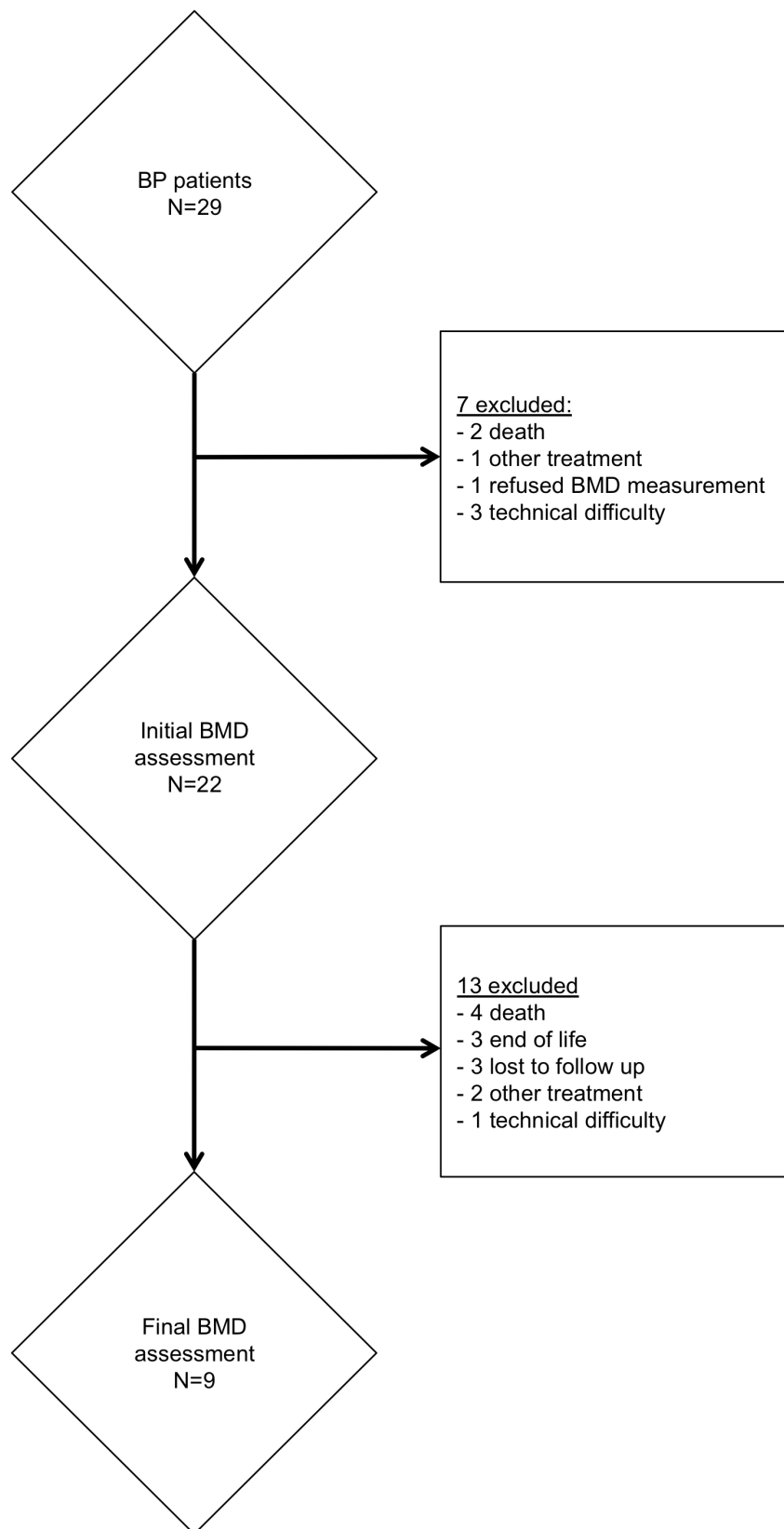
Figure 1 Flow chart

Figure 2 Representation of lumbar spine, femoral neck and hip BMD change, baseline BMD, and cumulative dose of clobetasol propionate.

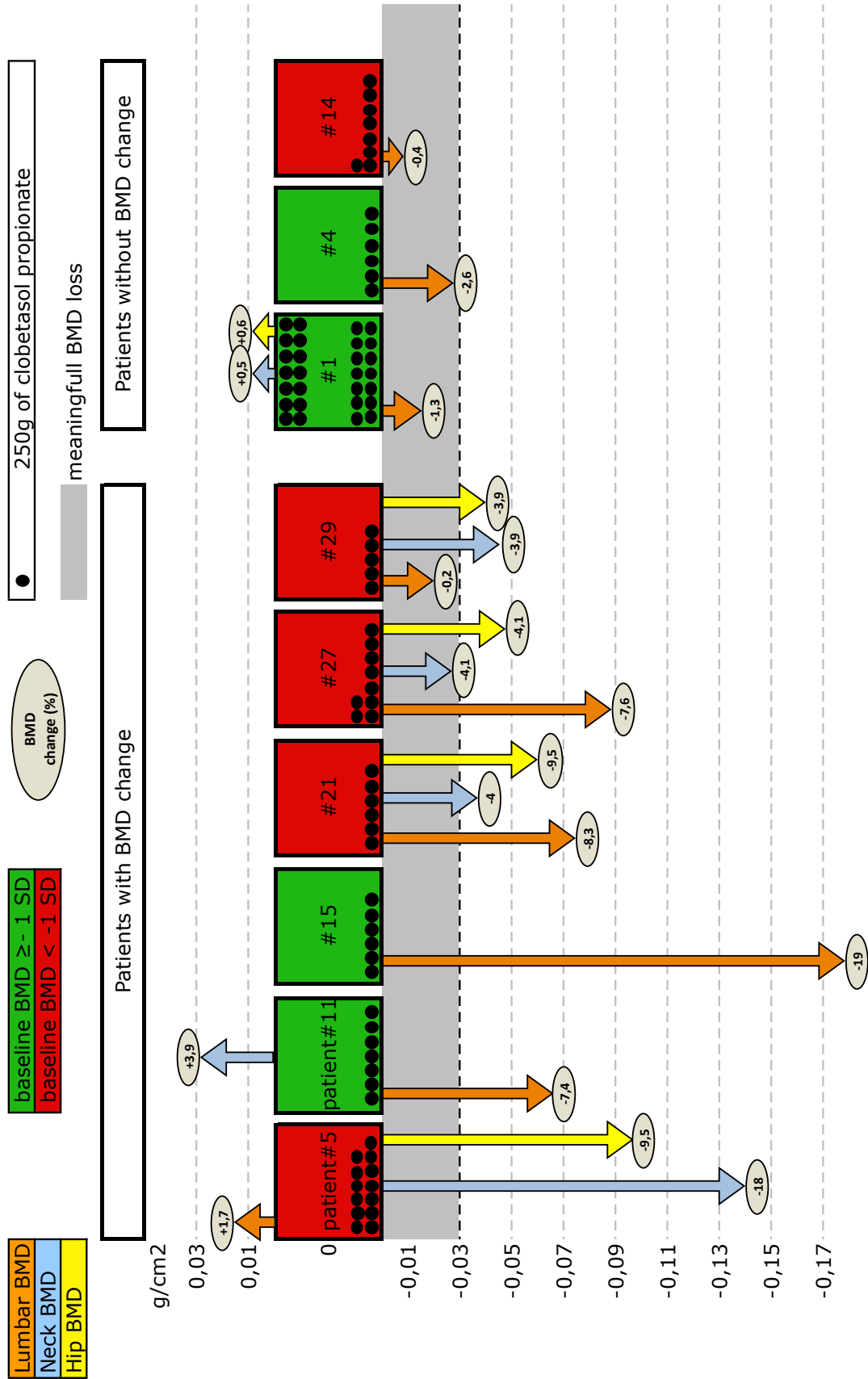


Figure 3 Correlation between lumbar spine variation (g/cm²) and dose of clobetasol propionate (g/kg/day)

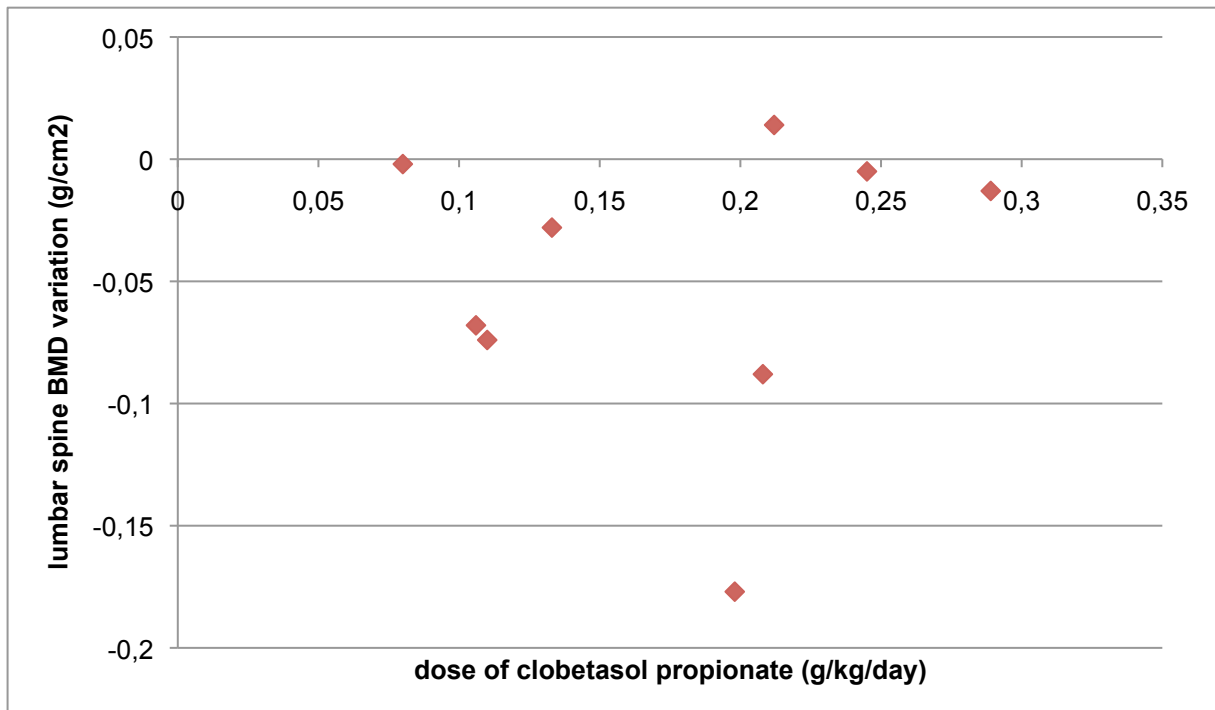


Table 1 Baseline characteristics

	Baseline characteristics n=22		
	nb of subjects		
Clinical			
Age (years)	22	86.1	± 7.2
Sex (n)	22		
Male n (%)		11	(50)
Female n (%)		11	(50)
Height (cm)	15	162.4	± 7.7
Weight (kg)	17	65.6	± 14.2
BMI (kg/m ²)	20	26.7	± 6
History of			
Oral corticosteroids n (%)	22	3	(14)
History of osteoporosis with fracture n (%)	22	5	(23)
Current smoker n (%)	22	2	(9)
Alcohol consumer n (%)	22	0	(0)
Neurological disorder n (%)	22	13	(59)
<10 bullae n (%)	22	11	(50)
Biological data			
Alkaline phosphate (U/l)	22	71.2	± 38.8
Calcium (mmol/l)	22	2.27	± 0.15
Urinary calcium (mmol/l)	15	1.95	± 1.9
Phosphate (mmol/l)	20	2.4	± 6.2
25-OHD (ng/ml)	22	15.2	± 8.5
PTH (pg/ml)	19	30.9	± 19.9
TSH (μU/ml)	21	2.2	± 1.6
8 am cortisol (ng/ml)	21	141	± 87
CTx (pmol/l)	21	4391	± 2176
P1NP (ng/ml)	21	58	± 57

Table 2 Baseline bone status

Baseline BMD	nb of subjects	Baseline characteristics	
		N=22	
Lumbar spine	20		
BMD (g/cm ²)		0.95	± 0.22
T score (SD)		- 0.93	± 1.94
Femoral neck	17		
BMD (g/cm ²)		0.66	± 0.17
T score (SD)		- 1.89	± 1.29
Hip	20		
BMD (g/cm ²)		0.82	± 0.22
T score (SD)		- 1.31	± 1.43
Baseline repartition of BMD			
Lumbar spine	20		
T score ≥ -1 n (%)		10	(50)
T score < -1 n (%)		10	(50)
Femoral neck	17		
T score ≥ -1 n (%)		5	(29)
T score < -1 n (%)		12	(71)
Hip	17		
T score ≥ -1 n (%)		10	(59)
T score < -1 n (%)		7	(41)

Table 3 Characteristics of patients with BMD change and patients without BMD change.

	Patients with BMD loss			Patients without BMD loss		
	nb of subjects	N=6		nb of subjects	N=3	
Clinical						
Age (years)	6	84.3	7.4	3	86.0	± 5.6
Sex	6			3		
Male n (%)		3	(50)		2	(67)
Female n (%)		3	(50)		1	(33)
Height (cm)	5	162.4	± 4.2	3	164.7	± 6.8
Weight (kg)	6	64.7	± 13	3	59.9	± 10.7
BMI (kg/cm ²)	5	26.3	± 5.5	3	24.3	± 4.2
History of						
Oral corticosteroids n (%)	6	0		3	0	
History of osteoporosis n (%)	6	2	(33)	3	1	(33)
Current smoker n (%)	6	0		3	0	
Alcohol consumer n (%)	6	0		3	0	
Neurological disorder n (%)	6	3	(50)	3	3	(100)
History of osteoporosis with fracture n (%)	6	2	(33)	3	1	(33)
<10 bullae n (%)	6	4	(66.7)	3	3	(100)
Treatment						
Cumulative dose of topical corticosteroid (g)	6	2036.7	± 851.6	3	3556.7	± 3292.2
Baseline biological data						
Alkaline phosphatase (UI/l)	6	72.7	± 56.2	3	86.0	± 13.7
Calcium (mmol/l)	6	2.34	± 0.1	3	2.09	± 0.29
Urinary calcium (mmol/l)	6	1.76	± 1.3	3	1.4	± 0.7
Phosphate (mmol/l)	6	5.7	± 11.4	3	1.2	± 0.1
25-OHD (ng/ml)	6	22.5	± 8.8	3	15.2	± 3.2
PTH (pg/ml)	4	42.8	± 29.1	2	13.0	± 1.4
TSH (μUI/ml)	6	3.3	± 2.6	2	1.3	± 0.1
8 am Cortisol (ng/ml)	6	205	± 46	2	113	± 62
CTx (pmol/l)	6	4651	± 3476	3	4490	± 2276
P1NP (ng/ml)	6	102	± 85	3	29	± 18
Baseline BMD						
Lumbar BMD (g/cm ²)	6	0.97	± 0.14	3	0.94	± 0.17
Femoral neck BMD (g/cm ²)	5	0.71	± 0.08	1	0.8	
Hip BMD (g/cm ²)	5	0.84	± 0.18	1	0.97	

U.F.R. DE MEDECINE DE RENNES

ROPARS Nolwenn – Evolution de la densité minérale osseuse chez des patients traités par dermocorticothérapie prolongée pour une pemphigoïde.

Evolution of bone mineral density in patients treated with high-dose topical corticosteroids for a bullous pemphigoid.

28 feuilles, 3 graphiques, 3 tableaux, 30 cm – Thèse : (Médecine); Rennes 1; 2016 ; N°

Résumé français

Introduction Les dermocorticoïdes (DC) utilisés à forte dose, peuvent avoir des effets secondaires systémiques (cushing, hyperglycémie) identiques à ceux observés avec la corticothérapie générale mais leurs effets secondaires osseux sont mal connus. Nous avons étudié l'évolution de la densité minérale osseuse (DMO) chez des patients traités par DC pour une pemphigoïde bulleuse (PB).

Matériel & Méthodes Une ostéodensitométrie et un bilan biologique étaient réalisés avant et après traitement par DC pour les patients suivis pour une PB au CHU de Rennes.

Résultats 29 patients ont eu une PB, 22 patients ont eu au moins une évaluation et 9 patients ont eu 2 évaluations. Nous avons observé une variation de la DMO supérieure à 0,03 g/cm² chez 6 des 9 patients. Il n'a pas été noté de corrélation avec la dose de DC.

Conclusion Ces résultats incitent à proposer des études de plus grande envergure pour l'analyse des liens entre DC et DMO chez les patients ayant une PB.

Rubrique de classement : Dermatologie - Thérapeutique

Mots-clés : Pemphigoïde Bulleuse ; Dermocorticothérapie ; Densité Minérale Osseuse

Mots-clés anglais MeSH : Bullous Pemphigoid; Topical Corticosteroids; Bone Mineral Density

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