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Montrouge, 12/20/2018

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Bullous pemphigoid in patients with DPP-4 inhibitors at the onset of disease: does this differ from common bullous pemphigoid?

published in:
European Journal of Dermatology, 2018, Volume 28, Numéro 5

John Libbey Eurotext

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of clinical findings based on dermoscopic examination, including follicular keratotic plugs.
Although the mechanisms involved in the positive effects of NB-UVB on LS are unknown, both anti-inflammatory and immunosuppressive effects of NB-UVB are likely to be operating. Kreuter *et al.* reported that the expression of matrix metalloprotease-1 (MMP-1) by dermal fibroblasts in extragenital LS was increased by NB-UVB [9]. In our case, follicular keratotic plugs and papules were significantly improved, suggesting that NB-UVB may also affect the epidermis in LS.
Our case suggests that NB-UVB therapy can be effective for extragenital (and possibly also anogenital) LS, and is an interesting alternative in case of failure with standard therapies. ■

Disclosure. *Financial support: none. Conflicts of interest: none.*

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doi:10.1684/ejd.2018.3393

Bullous pemphigoid in patients with DPP-4 inhibitors at the onset of disease: does this differ from common bullous pemphigoid?

During the last decade, dipeptidyl peptidase (DPP)-4 inhibitors have been associated with the development of bullous pemphigoid (BP). Usually, for drug-induced eruptions, the causative role of any medication has to be proven following cessation and re-administration; a re-challenge test that raises ethical concerns. Regarding the particular features of gliptin-associated BP, a number of different options are available. In the present study, we collected data from a tertiary centre in Northern Greece in order to define the clinical and immunological profile of patients who were taking gliptins at the time of BP diagnosis, and further compared this data with that of patients with classic BP.
A total of 142 patients with newly diagnosed BP who attended our outpatient clinic from September 2011 to May 2017 were consecutively selected to participate in this prospective cohort study. Diagnosis was based on histological and immunofluorescence techniques. Clinical severity was assessed based on BPDAI scores. Patients' age, gender, mucosal involvement, gliptin uptake, type of gliptin, and duration of uptake up to BP onset were recorded. Titres of anti-BP180 and anti-BP230 auto-antibodies, histological findings, and direct and indirect immunofluorescence findings were also recorded. Gliptin was discontinued at the time of BP diagnosis and switched to other antidiabetic drugs. Forty-seven patients (33.1%) were taking gliptin at the time of diagnosis. Patients' demographic, clinical, histological, and immunological characteristics are presented in *table 1*.
DPP-4 inhibitors were introduced for the treatment of type 2 diabetes mellitus in 2006 and are prescribed extensively worldwide [1]. A possible association with the development of BP was first described in 2012 by Scandalis *et al.* [2]. Since then, this issue has been discussed in a number of publications of case studies and series [1-6]. According to these reports, a broad range of time (45 days to 37 months) between initiation of gliptin and BP onset has been reported [1]. In our study, for 47 patients with gliptin-associated BP, this period ranged from five to 61 months (median: 23 months).
Does gliptin-associated pemphigoid differ from common BP? Izumi *et al*. described gliptin-associated pemphigoid as lacking oedematous erythema, histologically non-inflammatory, and with a different autoantibody profile targeting areas other than the NC16A domain [7]. On the other hand, most reported patients with possible gliptin-associated BP have typical clinical features as well as histological features including those based on direct immunofluorescence [1-7]. Fania *et al*. detected inflamed phenotypes and typical NC16A reactivity in a series of patients, underlining that the pathogenesis of DPP-4 inhibitor-induced BP has overlapping features with classic BP [8].
In our cohort, no significant differences were observed with regards to clinical presentation, mucosal involvement, severity, eosinophilic infiltration, or immunofluorescence between patients with common BP and gliptin-associated BP (*table 1*). BPDAI correlated with titres of BP180NC16a and BP230 autoantibodies in both groups. Additionally, the clinical course did not differ significantly with regards to clinical remission, and there was no statistically significant difference in the time to achieve minimal steroid dose. The only difference was the significantly higher number of relapses in patients with classic BP (*table 1*).
In all cases with gliptin-induced BP in the literature, excluding cases in which gliptin was withdrawn, steroids were mostly administered systemically [1]. In our patients, treatment schemes also did not differ.

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Table 1. Patients' demographic and clinical characteristics.

Characteristics	BP patients taking gliptin (*n* = 47)	Patients with common BP (*n* = 95)	*p* value
Age (years)			
Mean±SD	77.40±7.63	74.05±14.58	0.368
Median (Min-Max)	80.0 (45.0-88.0)	78.0 (5.0-94.0)	
Gender			
Male *n* (%)	23 (48.9)	46 (48.4)	0.954
Female *n* (%)	24 (51.1)	49 (51.6)	
CNS disorders			
Yes *n* (%)	10 (21.3)	16 (16.8)	0.645
No *n* (%)	37 (78.7)	79 (83.2)	
Mucosal involvement			
Yes *n* (%)	9 (19.1)	14 (14.7)	0.502
No *n* (%)	38 (80.9)	81 (85.3)	
BPDAI (0-360)			
Mean±SD	41.04±25.73	34.13±25.75	0.063
Median (Min-Max)	38.0 (2.0-144.0)	27.0 (1.0-121.0)	
Time to min maintenance dose (months)			
Mean±SD	3.46±2.01	3.25±1.89	0.578
Median (Min-Max)	3.0 (1.0-11.0)	2.7 (1.14-13.0)	
Recurrence			
Yes *n* (%)	9 (19.1)	41 (43.2)	**0.005**
No *n* (%)	38 (80.9)	54 (56.8)	
Anti-BP180 titres (U/mL)			
Mean±SD	75.50±84.10	49.46±78.16	0.270
Median (Min-Max)	27.8 (2.0-245.0)	18.0 (2.0-200.0)	
Anti-BP230 titres (U/mL)			
Mean±SD	20.45±29.94	21.33±37.11	0.519
Median (Min-Max)	12.0 (2.0-153.0)	11.0 (2.0-200.0)	
Anti-BP180			
Positive *n* (%)	27 (57.4)	46 (48.4)	0.311
Negative *n* (%)	20 (42.6)	49 (51.6)	
Anti-BP230			
Positive *n* (%)	10 (21.3)	14 (14.7)	0.328
Negative *n* (%)	37 (78.7)	81 (85.3)	
Histological findings			
Typical *n* (%)	31 (66.0)	60 (63.2)	0.744
Non-typical *n* (%)	16 (34.0)	35 (36.8)	
DIF findings			
Positive *n* (%)	43 (91.5)	85 (89.5)	0.705
Negative *n* (%)	4 (8.5)	10 (10.5)	
IIF findings			
Positive *n* (%)	29 (61.7)	42 (44.2)	0.05
Negative *n* (%)	18 (38.3)	53 (55.8)	

DIF: direct immunofluorescence; IIF: indirect immunofluorescence.

International concern regarding administration of DPP-4 inhibitors and induction of BP appears to be justified [9]. Moreover, as indicated by Fania *et al*., the prevalence of diabetes mellitus increased significantly in patients with BP after 2007, indicative of the addition of gliptins for the treatment of type 2 diabetes mellitus [8]. However, recent data by Schaffer *et al.* do not support an association between the onset of BP and use of DPP-4 inhibitors [10].

In elderly patients, age, drugs and neurological disorders are linked to a modified immune response against antigens of the basement membrane, indicating that BP is multifactorial [5]. In our population, neurological comorbidities did not significantly differ between the two groups, which would have confounded the induction of BP.

We conclude that DPP-4 inhibitors may contribute to the induction of BP in elderly patients, and clinicians should be aware of this association. Based on our findings, however, gliptin-associated BP should not be considered as a separate form of BP. ■

Disclosure. *Financial support: none. Conflicts of interest: none.*

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doi:10.1684/ejd.2018.3371

Pneumocystis jirovecii pneumonia infection in pemphigus patients treated with rituximab: an observational nationwide epidemiological study in Taiwan

Rituximab is gradually becoming the first-line treatment for pemphigus [1], however, it is debated whether rituximab can increase the risk of *Pneumocystis jirovecii pneumonia* (PJP) infection [2]. For patients with organ transplants, ANCA-positive vasculitis, and haematological malignancies, there is a high level of mortality and morbidity, and PJP prophylaxis is routinely used for such patients. A delayed

Table 1. Summary of pemphigus cases diagnosed with *Pneumocystis jirovecii pneumonia (PJP)* infection.

Study	Age	Sex	Disease duration	Underlying disease	Regimen of rituximab	Concomitant treatment	Doses of prednisolone (mg/day)	Onset of PJP (weeks)†	Outcome‡	Duration of hospitalization‡
Amber *et al*. [5]	40s	M	N/A	(-)	Biweekly ×2	N/A	20	8	Alive	N/A
Wei *et al* [6]	61	M	15 months	(-)	Weekly ×4	MMF	50	8	Deceased	4 weeks
Morrison [8]	37	M	4 years	(-)	Weekly ×4	CYS	10 to 20	16	Deceased	5 weeks
Shimanovich *et al* [9]	71	M	4 months	N/A	Weekly ×4	CYSMMF	N/A	16	Alive	N/A
Current study	58	M	N/A	(-)	Weekly ×4	AZA	40	10	Alive	9 weeks
	33	M	N/A	Diabetes mellitus	Weekly ×2	AZA	30	25	Alive	3 weeks

†*After the first dose of rituximab.*‡*Outcome following hospitalisation and treatment for pneumocystis infection.AZA: azathioprine; CYS: cyclophosphamide; MMF: mycophenolate mofetil; N/A: data not available.*

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