Bullous Pemphigoid/Pemphigus and administration of the Pfizer/BioNTech vaccine (Comirnaty®).

Introduction

The Pfizer/BioNTech vaccine (Comirnaty®) is a COVID-19-mRNA-vaccine (nucleoside modified). It is indicated for *active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.* [1] The nucleoside-modified messenger RNA in Comirnaty® is formulated in lipid nanoparticles, which enable delivery of the nonreplicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length Spike glycoprotein with two point mutations within the central helix. [1] Comirnaty® has been registered in Europe since December 21st, 2020.

Bullous skin diseases are a group of dermatoses characterized by blisters and bullae in the skin and mucous membranes. The most common are pemphigus and bullous pemphigoid (BP). Pemphigus and bullous pemphigoid are autoantibody-mediated blistering skin diseases. In pemphigus, keratinocytes in epidermis and mucous membranes lose cell-cell adhesion, and in pemphigoid, the basal keratinocytes lose adhesion to the basement membrane. Bullous pemphigoid is a more common disease than pemphigus [2].

Bullous pemphigoid is the most common heterogeneous subepidermal autoimmune blistering disease (incidence 7 per million person year) [3,4], with an increasing prevalence after the age of 70, although it can also occur in the younger. It is characterized by auto-antibodies against different structural proteins of the hemidesmosomes in the epidermal basement membrane zone (EBMZ). Bullous pemphigoid typically causes severe pruritus with predominantly cutaneous lesions consisting of tense (fluid filled) bullae, erythema, and urticarial plaques. Bullae may rupture forming crusted erosions.
Diagnosis is based on the clinical presentation, histopathologic and immunofluorescence features and immunoassays. Besides idiopathic cases, also cases with an iatrogenic origin (mainly drugs, but also including vaccines) have been reported. Most common are the DPP-4 inhibitors (gliptins) followed by the PD-1/PD-L1 inhibitors (immune checkpoint inhibitors), and to a lesser degree e.g. loop diuretics, penicillins, NSAIDs, and penicillamine [3,4,5].

Bullous pemphigoid is the result of an attack on the EBMZ by predominantly IgG immunoglobulins (autoantibodies) and activated T lymphocytes (white blood cells). The predominant target is the protein BP180 (also called Type XVII collagen), and less frequently BP230 (a plakin). These proteins are within the NC16A domain of collagen XVII. They are associated with the hemidesmosomes, structures that ensure the epidermal keratinocyte cells stick to the dermis to make a waterproof seal. The binding of the autoantibodies to the proteins and release of cytokines from the T cells lead to complement activation, recruitment of acute inflammatory cells and the release of proteolytic enzymes. These destroy the hemidesmosomes and cause the formation of subepidermal blisters [4].

Several mechanisms have been postulated for iatrogenic BP, a.o. the capability of some thiol-based drugs for direct splitting of the skin, independently of the formation of antibodies. In vaccine-induced BP it has been postulated that some individuals harbor subclinical BP or undiagnosed eczematous-variant BP that was unmasked by vaccination and that in those with more rapid development (e.g. after the first dose), transient bystander immune activation invigorates an existing subclinical autoreactivity, while in cases with a longer latency, a new cutaneous response may be primed [6].

Reports

In the period from January 6th, 2021 until July 26th, 2021 the Netherlands Pharmacovigilance Centre Lareb received 4 reports on bullous pemphigoid/pemphigus associated with administration of Comirnaty® (table1).

Table 1. Reports of bullous pemphigoid associated with Comirnaty®

No	ID, sex, age class, primary source	Drug	Indication	Concomitant medication	Reported ADRs	Latency after start	Outcome
1	NL-LRB-00627057, male, 80-90 Years, Physician	Comirnaty®	COVID 19 immunisation, 2nd vaccination	Clobetasole, Miconazole, Triamcinolonacetonide, Zincoxide, Dabigatran, Fosinopril Tablet 10Mg, Metoprolol, Simvastatin, Dutasteride/Tamsulosine	Pemphigus	5 days	
2	NL-LRB-00441821, male, 50-60 Years, Physician	Comirnaty®	COVID 19 immunisation, 1st vaccination	Aripiprazole, Quetiapine, Lorazepam, Rivastigmine	Bullous pemphigoid	1 Days	Not Recovered
3	NL-LRB-00471153, male, 70-80 Years, Physician	Comirnaty®	COVID 19 immunisation, 2nd vaccination	Clozapine, Acetylsalicylic acid, Finasteride Levodopa/Benserazide, Levothyroxine, Omeprazol Rosuvastatin	Bullous pemphigoid, Fatigue, Malaise	2 Days	Recovering
4	NL-LRB-00629717, female, 80-90 Years, Consumer or other non health professional	Comirnaty®	COVID 19 immunisation, 2nd vaccination	Salbutamol, unknown tricyclic antidepressant	Bullous pemphigoid, Coma	12 Days	Died weeks later, unknown cause of death

Additional information on the cases is listed below.
Case 1: The patient experienced blisters on toes and right foot, later also (less intense) the left side and digits IV and V of the right hand. Later also hands and lower arms. Legs are under control because of treatment by dermatologist, but lower arms are still under treatment. The patient had aphthae in the mouth. Skin biopsy right arm: Subcorneal/intra-epidermal blister with eosinophilia and bacterial colonies. Immunofluorescence (IF) examination showed convincing pemphigus pattern. Ultrasound examination: slight grow of renal cell carcinoma. No further indication for malignity
Case 2: There was extensive blistering on the legs and feet. Bullous pemphigoid was treated with prednisolone 30 mg 1 dd (for 10 days followed by tapering of dose) and clobetasole 2 dd. Wound care was initiated for blisters that were open. At the time of reporting, the patient had not recovered from bullous pemphigoid. There were no previous signs of pruritus or common cold symptoms and no mucous involvement. No auto-immune disorders in medical history. No biopsy or IF was performed due to the patients fragile condition (progressive Lewy Body Dementia).
Case 3: According to the dermatologist, the fluid filled blisters on the patient's hand and ear were diagnosed as bullous pemphigoid, however no biopsy has been performed. The patient was treated with clobetasole. Past drug therapy: covid-19 vaccin pfizer injvlst with no adverse reaction.
Case 4. Bullous pemphigoid was diagnosed by a dermatologist (skin biopsy and IF) and initially treated with prednisone and thereafter with clobetasole, pregabaline and paracetamol. The first symptoms occurred in February 2021; The bullous pemphigoid became worse over time and the blisters kept opening up. During the use of clobetasole, the patient developed a Cushing syndrome. On June 7th patient's condition worsened and she became comatose. She died weeks later, unknown cause of death.

Other sources of information

SmPC

The SmPC of Comirnaty® does not mention bullous pemphigoid or pemphigus vulgaris as an adverse reaction [1].

Literature

Bullous pemphigoid, including flare-up of an existing condition, has been described in case-reports associated with Covid-19 vaccination with mRNA vaccines from Pfizer and Moderna. Damiani, et al. [7] have described the five cases below of autoimmune bullous diseases (AIBDs). See the table below from their article.

Table 1 Data of AIBD-affected patients

	Sex/age	AIBD	Previous medications for AIBDs	Vaccine (2 doses)	New medications for flare up	Anti-SARS-CoV-2 S1-RBD IgG >50 UI/L
1	F/75	BP	Oral prednisone	Moderna	Oral prednisone	Yes
2	M/40	PV	Rituximab	Moderna	Oral prednisone Mycophenolate mofetil	Yes
3	M/84	BP	Oral prednisone Azathioprine	Moderna	Oral prednisone*	Yes
4	F/82	BP	Oral prednisone Mycophenolate mofetil	Pfizer	Oral prednisone	Yes
5	M/80	PV	Oral prednisone Mycophenolate mofetil	Pfizer	Oral prednisone	Yes

*Treatment started only after the 2nd dose.

The American Academy of Dermatology/International League of Dermatological Societies COVID-19 Dermatology registry has collected 733 cases of skin reactions reported after Covid-19 vaccination between December 24 and April 25, 2021. A total of 7 females and 5 males (median age 82.5-years; range 42-97 years), without a history of bullous pemphigoid (BP) or autoimmunity, developed inflammatory vesicles and bullae a median of 7 days (range 12 hours-21 days) after receiving the first or second dose of a Covid-19 mRNA vaccine. All were evaluated by dermatologists, who recorded cutaneous bullae distant from the injection site and skin biopsies demonstrating subepidermal separation and dermal infiltrates with eosinophils. An additional 13th patient with a history of BP had worsened disease but did not undergo further testing [6]. See the table below by Tomayko et al. [6].

TABLE I. Diagnosis, treatment, and disease outcomes of patients with BP arising after COVID-19 vaccination

Age (y)/ Sex/Vaccine	History*	Latency to blisters†	H&E staining‡	DIF at DEJ	BP180/230§	Treatment	Outcome
97/F/Pfizer	Psoriasis	(Dose 2) on d 2	+	IgG/C3/IgA SSS, roof	130/81	TCS, DCN, NAM	Improving at wk 2
75/M/Pfizer	Eczematous dermatitis	(Dose 2) on d 10; (dose 1 worsened dermatitis)	+	C3	169/nd	OCS, TCS, DCN, NAM	Improving at wk 3, no longer taking an OCS
64/M/Pfizer	None	(Dose 2) on d 14	+	C3; SSS, floor	26/82	TCS	Improving at wk 4
82/M/Pfizer	Dermatitis	(Dose 2) on d 1; (dose 1 worsened dermatitis)	+	IgG/C3/weak IgA SSS, roof	Neg/Neg	TCS	Resolved at wk 2
95/F/Pfizer	Nonmelanoma skin cancer	(Dose 1) on d 5; (dose 2 no flare)	+	IgG/C3/weak IgA SSS, roof	Neg/Neg	TCS, DCN, NAM	Resolved at wk 8, no longer taking DCN, NAM
87/M/Moderna	Stasis dermatitis, Alzheimer disease	(Dose 2) on d 21; (dose 1 worsened dermatitis)	+	C3	+/+	OCS, DCN, NAM	Ongoing at d 105
42/F/Moderna	Hand eczema	(Dose 2) on d 3	+	IgG/C3/weak granular IgM	>200/59	IMCS, TCS, IVCS	Ongoing at d 23, improving with CS
85/M/Pfizer	Dementia	(Dose 1) on d 5; (dose 2 withheld)	+	IgG/C3	nd	OCS	Ongoing at d 59¶
83/F/Moderna	Raynaud syndrome, major depression	(Dose 1) on d 8; (dose 2 withheld)	+	Neg; IIF result Neg	Neg/Neg	OCS, TCS	Ongoing at mo 2
66/F/Pfizer	Atopic dermatitis	(Dose 1) on d 7; (dose 2) mild flare‖	+	Neg; IIF result Neg	Neg/Neg	OCS, TCS	Resolved at wk 3
70/F/Moderna	Herpes simplex	(Dose 1) on d 9; (dose 2) no reported flare	+	Neg	nd	OCS	Resolved at 1d 5 d
83/F/Pfizer	Dementia	(Dose 2) on d 7	+	nd	nd	OCS, TCS, DCN, NAM	Ongoing at wk 6
83/M/Pfizer	BP¶	(Dose 1) on d 7; (dose 2 withheld)	nd	nd	nd	OCS, TCS	Ongoing at d 45

DCN, Doxycycline; *DEJ*, dermal epidermal junction; *DIF*, direct immunofluorescence histology; *H&E*, hematoxylin and eosin; *F*, female; *IIF*, indirect immunofluorescence; *IMCS*, intramuscular corticosteroid; *IVCS*, intravenous corticosteroid; *M*, male; *Moderna*, Moderna COVID-19 mRNA vaccine; *NAM*, nicotinamide; *Neg*, negative; *OCS*, oral corticosteroid; *nd*, no data; *Pfizer*, Pfizer COVID-19 mRNA vaccine; *SSS*, salt split skin immunofluorescence histology; *TCS*, topical corticosteroid; *Vac*, vaccine.
*Dermatology history, medical conditions associated with BP.
†Blisters were distant from the immunization site in all and widespread unless otherwise noted (by the symbol ‖).
‡Consistent with BP (subepidermal split, infiltrate with eosinophils).
§Serum IgG level according to ELISA, U/mL. Test results were considered negative if BP180 was less than 14 U/mL and BP230 was less than 9 U/mL.
‖Blisters on arms, hands, and lips only after dose 1. A few new blisters on the hands after dose 2.
¶BP was diagnosed in October 2020 (before vaccination). The BP was under control without oral medication before vaccination and flared 5 days after vaccination, requiring systemic treatment. A repeat diagnostic biopsy was not performed.

Bullous pemphigoid and pemphigus vulgaris have also been associated with COVID-19 infection [8,9].

Databases

Table 1. Reports of bullous pemphigoid and Pemphigus associated with the administration Covid-19 vaccines in the Vigibase [10].

Vaccine Brand	MedDRA® PT name	Number of reports
Comirnaty, Pfizer BioNTech	Pemphigoid	53
AstraZeneca	Pemphigoid	25
Comirnaty, Pfizer BioNTech	Pemphigus	11
Moderna	Pemphigoid	11
AstraZeneca	Pemphigus	6

On 20-06-2021 the number of reports in the global Vigibase® for Comirnaty was 428,458, for the Astrazeneca vaccine Vaxzevria® 441,279 and for Moderna Spikevax® 189,299.

Prescription data

Until July 4 2021 approximately 11,8 million vaccinations with Comirnaty® were given [11].

Mechanism

Tomayko et al [6] postulate the following in their case-series; 'It is possible that some individuals who developed Bullous Pemphigoid (BP) after Covid-19 immunization harbored subclinical BP or undiagnosed eczematous-variant BP that was unmasked by vaccination. It is conceivable that in those with more rapid development of bullae (eg, after the first dose), transient bystander immune activation invigorated an existing subclinical autoreactivity. In those with more delayed kinetics, a new cutaneous response may have been primed.'

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 3 reports of bullous pemphigoid (BP) and one of Pemphigus after administration of Comirnaty®. Both Pemphigus and BP are autoimmune blistering skin diseases. Both are mediated by autoantibodies, but their mechanisms of pathophysiology and their pathologies are different [2]. Although BP en pemphigus are two distinct clinical entities, they share similar characteristics and show a close resemblance.

Presently there are no reports for BP or Pemphigus for any of the other vaccines used in the Netherlands. In the global Vigibase® most reports on bullous pemphigoid concern Comirnaty®, although this does not take into account the number of vaccinated persons. In the literature BP is described after 1st and 2nd vaccination with mRNA vaccines. The number of described cases is still limited and other causes than vaccination with Comirnaty® may be possible. Some of the concomitant medication the patients are using such as statins is possibly associated with drug-induced bullous pemphigoid [4]. In addition, not all cases describe a diagnosis performed with immunoassays and IF.

Bullous pemphigoid can be a serious condition, particularly when widespread or resistant to treatment. Morbidity and mortality can result from skin infections and sepsis. Even though bullous pemphigoid is the most common autoimmune blistering disease, the relation between vaccination with Comirnaty® and this reaction should be further investigated seeing the serious nature of this condition.

Reference list

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