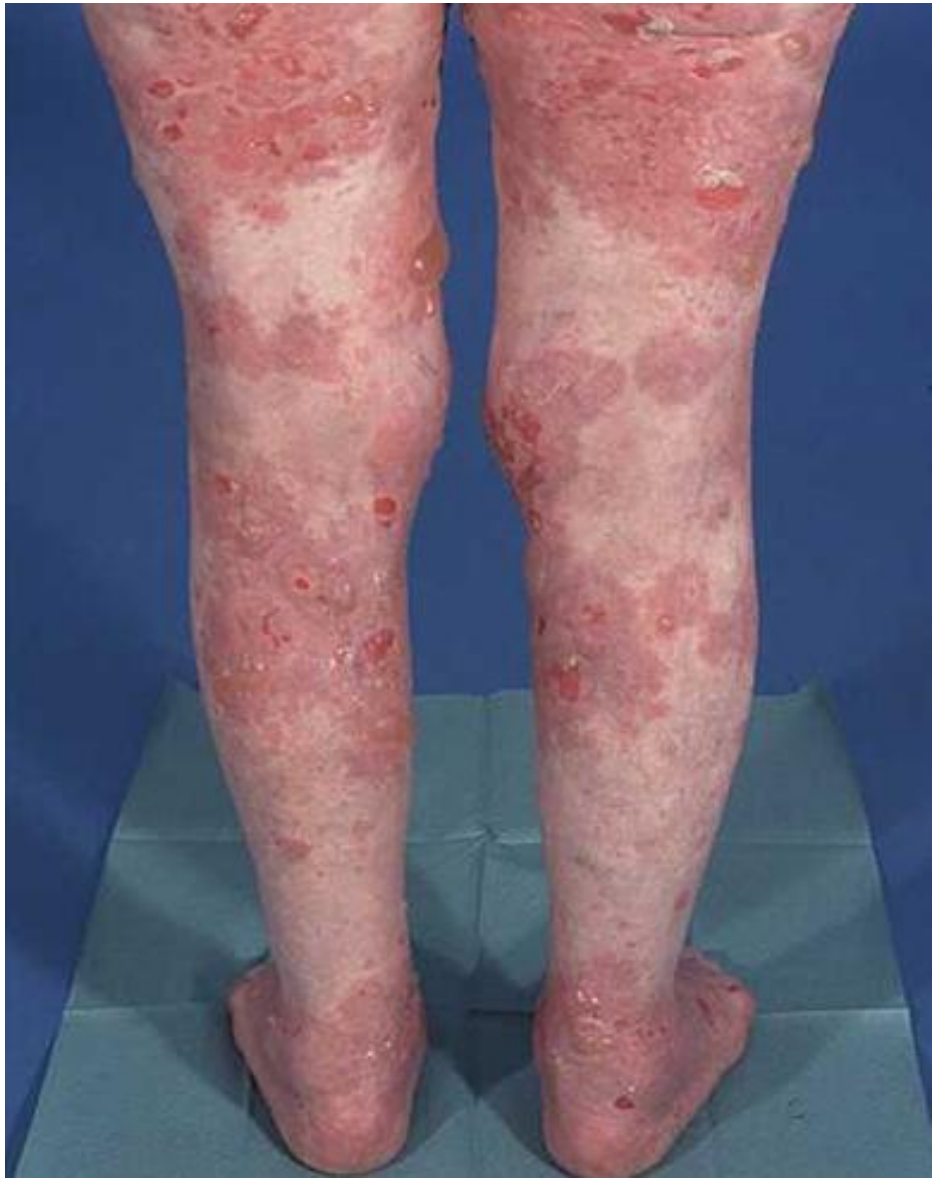
AUTOIMMUNE BLISTERING SKIN DISEASES IN FINLAND

Kaisa Tasanen
Department of Dermatology
Oulu University Hospital and University of Oulu
Finland

CONFLICT OF INTEREST:

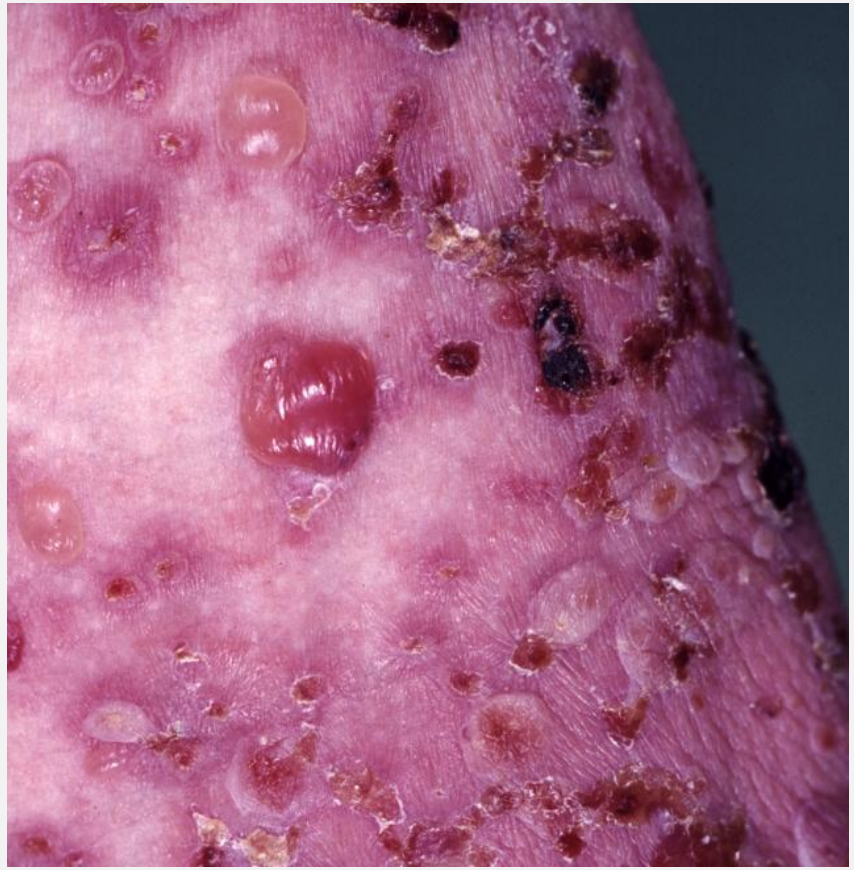
EDUCATIONAL GRANTS/HONORARIA
-Novartis
-Takeda
-Johnson & Johnson
-Sanofi

MEMBERSHIPS IN ADVISORY BOARDS
-Abbvie
-Novartis
-UCB Pharma



CONTENT

- Epidemiology of autoimmune blistering skin diseases in Finland
- Bullous pemphigoid (BP)
  - Risk factors
    - Neurological diseases
    - Medications
    - Malignancies
  - Treatment
  - Mortality
- Mucous membrane pemphigoid (MMP)



FINNISH NATIONAL HEALTH REGISTRIES

THL

- Finnish Care Register for Health Care (ICD-codes)
  - In-patients visits 1969-
  - Out-patients visits 1998-

Kela

- Data on all re-imbursed medications

Vildagliptin Significantly Increases the Risk of Bullous Pemphigoid: A Finnish Nationwide Registry Study

Outi Varpuluoma[1,2], Anna-Kaisa Försti[1,2], Jari Jokelainen[3,4], Miia Turpeinen[5,6], Markku Timonen[4], Laura Huilaja[1,2] and Kaisa Tasanen[1,2,*]

Journal of Investigative Dermatology (2018) **138,** 1659–1661; doi:10.1016/j.jid.2018.01.027

Epidemiology and Comorbidities of Mucous Membrane Pemphigoid: A National Cohort Study

Päivi Leisti[1], Laura Huilaja[1], Jari Jokelainen[2], Outi Varpuluoma[1] and Kaisa Tasanen[1,*]

Journal of Investigative Dermatology (2024) **144,** 2078–2080; doi: 10.1016/j.jid.2024.02.008

Risk factors of hand eczema: A population-based study among 900 subjects

Marjut Koskelo[1] | Suvi-Päivikki Sinikumpu[1] | Jari Jokelainen[2] | Laura Huilaja[1]

Contact Dermatitis. 2022;87:485–491.

Male patients with rosacea have increased risk for migraine: a population-based study

S-P. Sinikumpu[1,2], H. Vähänikkilä[3], J. Jokelainen[3], K. Tasanen[1,2] and L. Huilaja[1]

British Journal of Dermatology (2021) **185**, pp1047–1076

Atopic Dermatitis Is Associated with Dermatitis Herpetiformis and Celiac Disease in Children

Journal of Investigative Dermatology (2021) **141,** 191–193; doi:10.1016/j.jid.2020.05.091

Saana Kauppi[1,2], Jari Jokelainen[3], Markku Timonen[4], Kaisa Tasanen[1,2,*] and Laura Huilaja[1,2]

Risk of Non-cutaneous Cancers in Individuals with Basal Cell Carcinoma: A Population-based Cohort Study

Hanna KURU[1,2], Jari JOKELAINEN[3,4], Kaisa TASANEN[1,2] and Laura HUILAJA[1,2]
[1]Department of Dermatology, University Hospital of Oulu, [2]Medical Research Center, PEDEGO Research Group, University of Oulu, [3]Northern Finland Birth Cohorts, Arctic Biobank, Infrastructure for Population Studies, Faculty of Medicine, University of Oulu and [4]Unit of General Practice, Oulu University Hospital, Oulu, Finland

Acta Derm Venereol 2022; 102: adv00826.

Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis

Eeva Sliz, PhD,[a,b] Laura Huilaja, MD, PhD,[c,d] Anu Pasanen, PhD,[c,d,e,f] Triin Laisk, PhD,[g] Ene Reimann, PhD,[g] Reedik Mägi, PhD,[g] FinnGen,* and Estonian Biobank Research Team,‡ Katariina Hannula-Jouppi, MD, PhD,[h,i,j,k] Sirkku Peltonen, MD, PhD,[l,m,n,o] Teea Salmi, MD, PhD,[p,q] Leena Koulu, MD, PhD,[l,m] Kaisa Tasanen, MD, PhD,[c,d§] and Johannes Kettunen, PhD[a,b§]
Oulu, Helsinki, Turku, and Tampere, Finland; Tartu, Estonia; and Gothenburg, Sweden

J ALLERGY CLIN IMMUNOL
MARCH 2022

Juvenile idiopathic arthritis in children and adolescents with atopic dermatitis: A Finnish nationwide registry study

Paula L. Keskitalo, MD,[a,b] Jari Jokelainen, MSc,[c] Kaisa Tasanen, MD, PhD,[b,d] Suvi-Päivikki Sinikumpu, MD, PhD,[b,d] and Laura Huilaja, MD, PhD.[b,d]

J Am Acad Dermatol
May 2023

Adult Patients with Atopic Eczema have a High Burden of Psychiatric Disease: A Finnish Nationwide Registry Study

Saana KAUPPI[1,2], Jari JOKELAINEN[3,4], Markku TIMONEN[4], Kaisa TASANEN[1,2] and Laura HUILAJA[1,2]
[1]PEDEGO Research Unit, University of Oulu, [2]Department of Dermatology and Medical Research Center Oulu, [3]Unit of General Practice, Oulu University Hospital, and [4]Center for Life Course Epidemiology and Systems Medicine, University of Oulu, Oulu, Finland

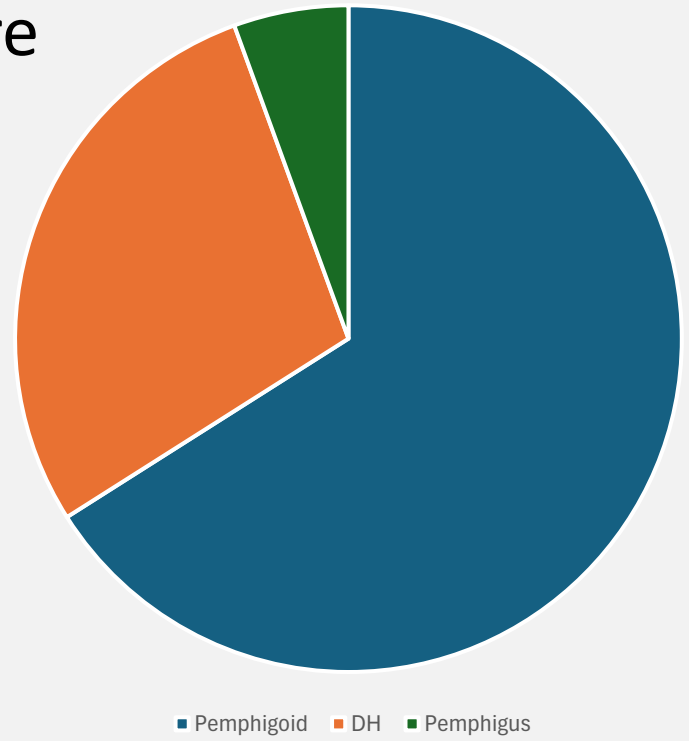
Acta Derm Venereol 2019; 99: 647–651

AUTOIMMUNE BLISTERING SKIN DISEASES IN FINLAND

The Finnish Care Register for Health Care database between 1996-2022:

8717 patients with AIBD

- 5754 pemphigoid cases
- 2478 dermatitis herpetiformis cases
- 485 pemphigus cases



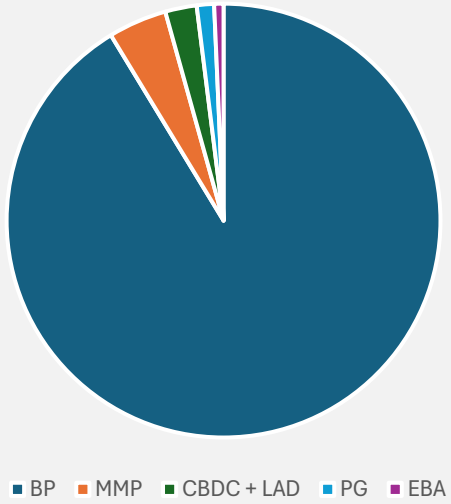
Veikkolainen et al., unpublished

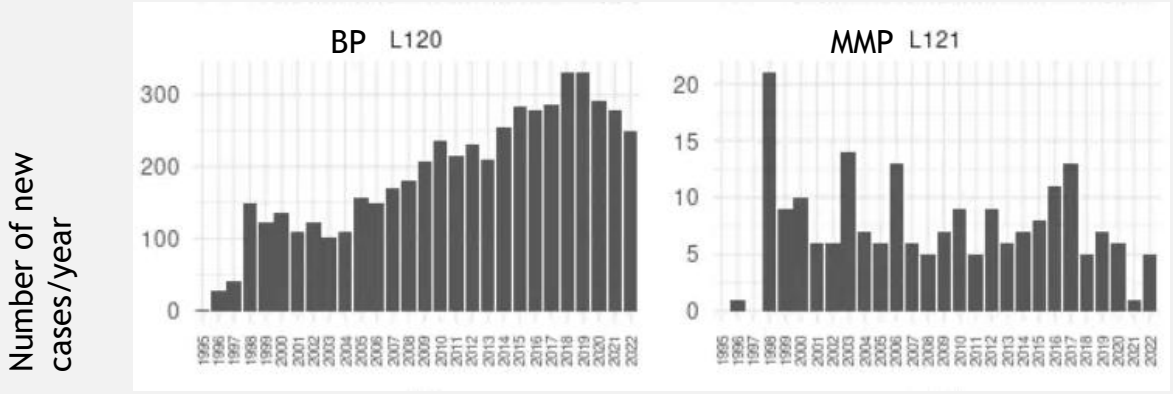
PEMPHIGOID DISEASES IN FINLAND

The Finnish Care Register for Health Care database between 1996-2022:

5754 pemphigoid cases

- 5254 BP cases
- 251 MMP cases
- 135 Linear IgA dermatosis/chronic bullous disease of childhood
- 76 gestational pemphigoid cases
- 40 epidermolysis bullosa acquisita cases
- p200 pemphigoid??





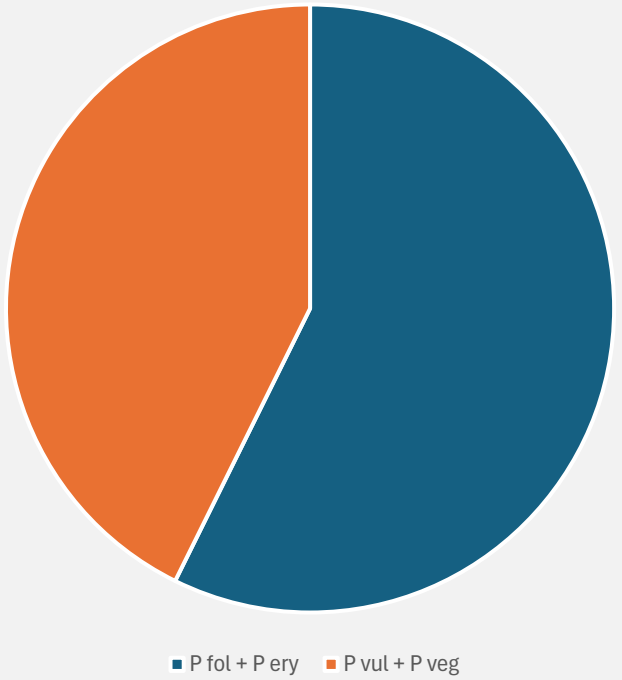
Veikkolainen et al., unpublished

PEMPHIGUS DISEASES IN FINLAND

The Finnish Care Register for Health Care database between 1996-2022:

485 pemphigus cases

- 190 p. foliaceus cases
- 88 p. erythematosus cases
- 193 p. vulgaris cases
- 14 p. vegetans cases



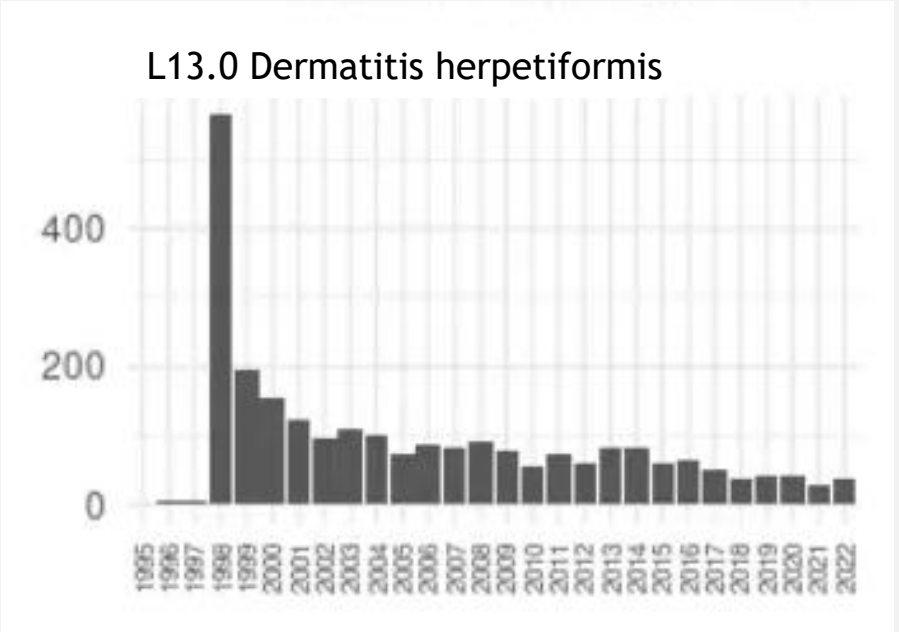
Veikkolainen et al., unpublished

DERMATITIS HERPETIFORMIS IN FINLAND

The Finnish Care Register for Health Care database between 1996-2022:

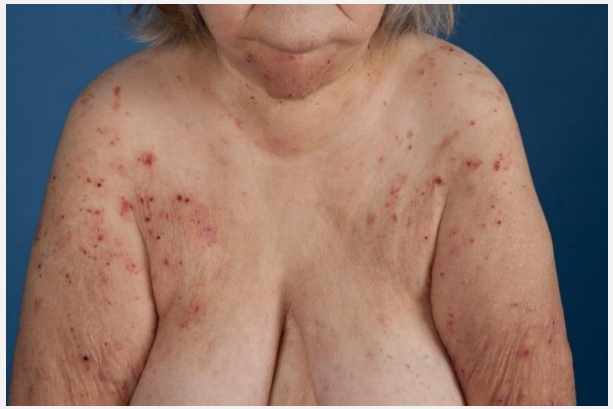
2478 DH cases

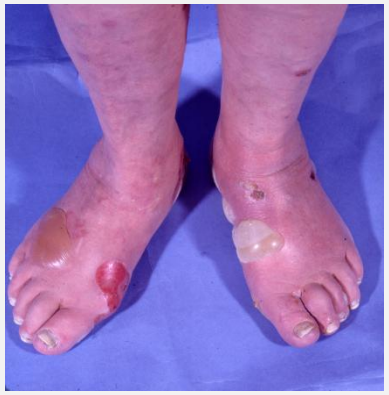
- Number of new cases has decreased

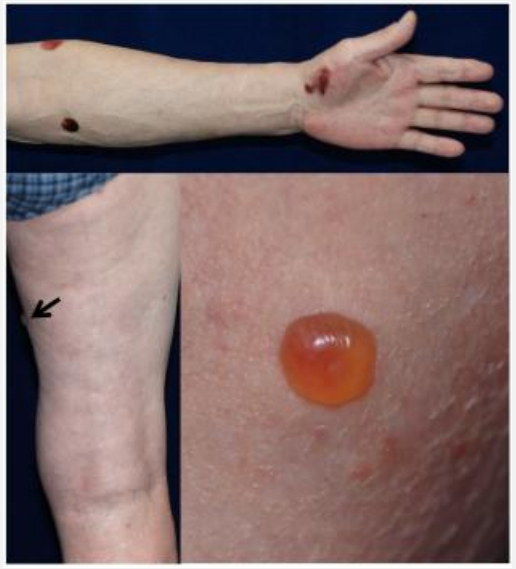


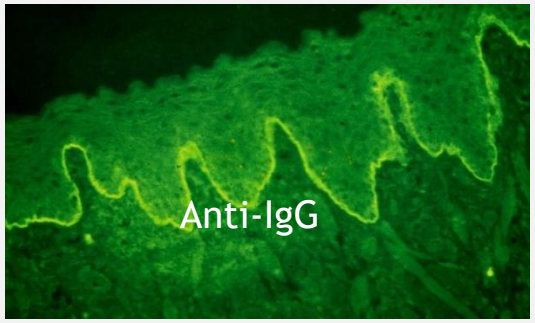
Veikkolainen et al., unpublished

BULLOUS PEMPHIGOID (BP)





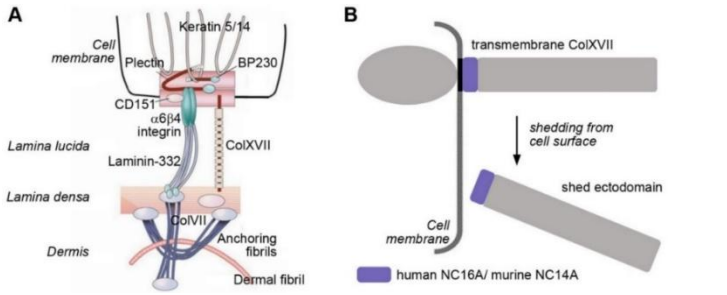


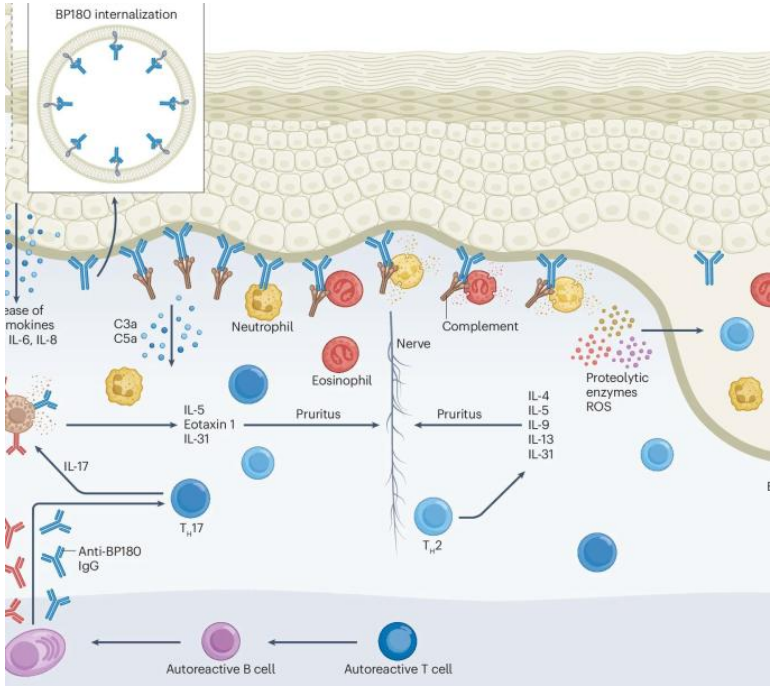


Tasanen et al, Front Immunol, 2019

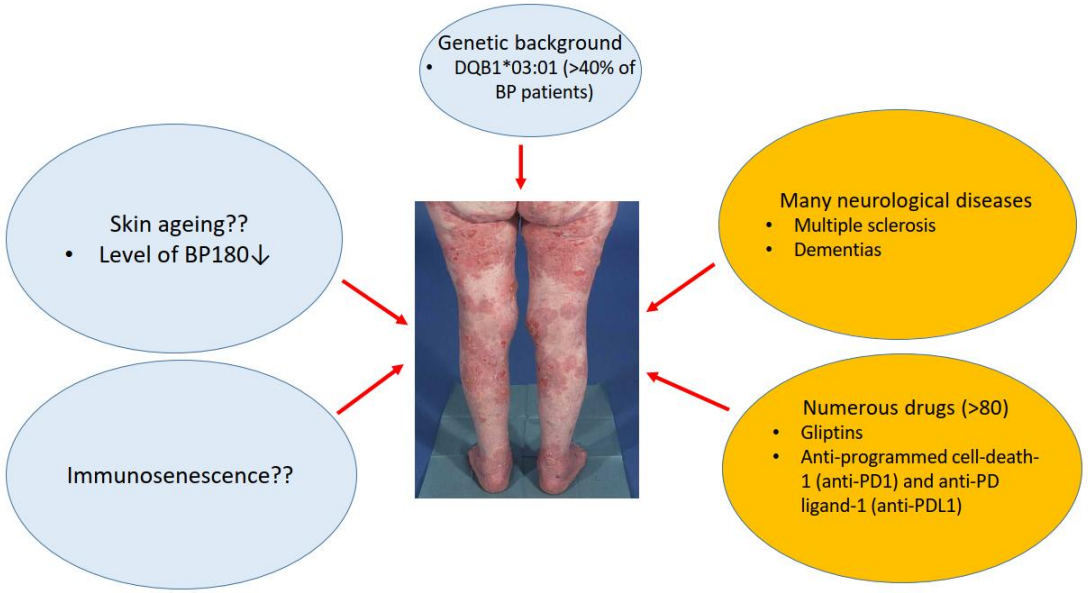
- BP onset is usually seen in patients who are in their late 70s
- Incidence↑↑ (4-66/1 milj./year)
- First symptom is often pruritus
- Localized or generalized excoritated, eczematous, papular and/or fixed urticarial lesions, generalized edematous erythema and/or blisters
- Up to 20 % patients have no blisters
- Mucosal symptoms in 10-20 % of patients
- Golden standard of diagnostics: DIF, also BP180-NC16A ELISA widely used

BP AUTOANTIBODIES TARGET BP180 (COLLAGEN XVII) AND BP230





WHAT TRIGGERS THE BREAKAGE OF IMMUNOLOGICAL TOLERANCE AGAINST BP180?



Akbarialiabad et al, Nature Review Diseases Primers, 2025

ASSOCIATION BETWEEN BP AND NEUROLOGICAL AND PSYCHIATRIC DISEASES

BP cases	Years	Disorders with a statistically significant association with BP	Database/ population	First author, year, country
13342	2002-2012	Multiple sclerosis, dementia, paralysis, neuropathy, Parkinson's disease, epilepsy, psychoses, depression	National Inpatient Sample	Ren, 2017, the USA
4524	1987-2013	Multiple sclerosis, dementia, Parkinson's disease, epilepsy, stroke, schizophrenia, schizotypal and delusional disorders, personality disorder	National Finnish Care Register for Health Care	Försti, 2016, Finland
3485	1997-2008	Stroke, dementia, Parkinson's disease, epilepsy, schizophrenia, psoriasis	National Health Insurance Research Database	Chen, 2011, Taiwan
3281	1977-2015	Multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke	Danish National Patient Registry	Kibsgaard 2017, Denmark
868	1996-2006	Stroke, dementia, Parkinson's disease, multiple sclerosis, epilepsy	National, General Practice Database	Langan, 2011, the UK

BP180 and the neural isoform of BP230 are expressed in the brain

HYPOTHESIS: Neuroinflammation could lead to a cross-reactive immunoresponse between neural and cutaneous antigens

REVIEW ARTICLE

Bullous pemphigoid and its association with neurological diseases: a systematic review and meta-analysis

Y.C. Lai,[1,†] Y.W. Yew,[2,†], W.C. Lambert[1,*]

[1]Department of Dermatology, Rutgers New Jersey Medical School, Newark, NJ, USA
[2]National Skin Centre, Singapore
*Correspondence: W.C. Lambert. E-mail: lamberwc@njms.rutgers.edu

- Any neurological disease (RR 4.93, 95 % CI 3.62-6.70)
- Multiple sclerosis (MS) (RR 12.40, 95 % CI 6.64-23.17)
- Dementia (RR 4.46, 95 % CI 3.23-6.16)
- Parkinson's disease (RR 3.42, 95 % 3.01-3.87)
- Epilepsy (RR 2.98, 95 % 1.42-6.28)
- Stroke (RR 2.68, 95 % 2.07-4.46)

BP ANTIBODIES ARE FOUND IN PATIENTS WITH DEMENTIA

Neurological disease	n (patients/controls)	Average age of patients/controls (years)	BP180 NC16A ELISA Number of positive cases (patients/controls)	BP230 ELISA Number of positive cases (patients/controls)	Western blot analysis	Indirect immunofluorescence (IIF) analysis	First author, year
Dementia	69/69	84/84	4/0, p=0.04	nd	All four BP180 ELISA positive samples and one additional dementia samples recognized BP180 and BP230 in human placenta extract.	All dementia and control samples were tested using IIF. Four BP180 ELISA positive samples and one additional dementia samples were positive.	Foureur et al, 2006
Dementia	26/23	na	1/0	1/1	Five patient samples recognized intracellular recombinant BP180 and one recombinant extracellular BP180. BP230 was not tested.	IIF analysis of a subgroup of Western blot positive samples (n=4) were negative.	Messingham et al, 2016
Alzheimer's disease	115/40	72.0/66.8	20/1, p=0.019	14/3, ns	All BP180 ELISA positive patient samples (n=20) recognized the full-length recombinant BP180. BP230 was not tested.	IIF analysis of 18 BP180 ELISA and Western blot positive samples were negative.	Kokkonen et al, 2017
Alzheimer's disease	48/50	72.5/72.8	23/4, p<0.0001	16 /11, ns	9 out of 23 AD samples recognized the cutaneous and 11 out of 23 the brain-derived full-length BP80	IIF analysis of 31 AD and 14 control samples were negative	Wang et al, 2021

Modified from Försti et al, Exp Dermatol, 2017

BP ANTIBODIES ARE NOT FOUND IN PATIENTS WITH PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS

Neurological disease	n (patients/ controls)	Average age of patients/ controls (years)	BP180 NC16A ELISA Number of positive cases (patients/ controls)	BP230 ELISA Number of positive cases (patients/ controls)	Western blot analysis	Indirect immunofluorescence (IIF) analysis	First author, year
Parkinson's disease	24/23	na	1/0	1/1	Two patient samples recognized intracellular recombinant BP180 and seven extracellular recombinant BP180. BP230 was not tested.	IIF analysis of a subgroup of Western blot positive samples (n=4) were negative.	Messingham et al, 2016
Parkinson's disease	75/75 50/65	63.1/63.1 63.5/>70	0/2 2/1	1/2 1/6	All the patient and control samples were negative in immunoblotting against cell-derived BP180 and laminin 332.	All dementia (n=125) and control samples (n=140) were tested using indirect immunofluorescence analysis. Two control samples were positive.	Recke et al, 2016
Multiple sclerosis	50/65	33.0/>70	0/1	0/6	All the patient and control samples were negative in immunoblotting against cell-derived BP180 and laminin 332.	All multiple sclerosis (n=50) and control samples (n=140) were tested using indirect immunofluorescence analysis. Two control samples were positive.	Recke et al, 2016
Multiple sclerosis	140/140	49.4/49.6	11/2, ns	6/nd	30/56 MS sera recognized the recombinant full-length BP180.	nd	Tuusa et al, 2019

Modified from Försti et al, Exp Dermatol, 2017

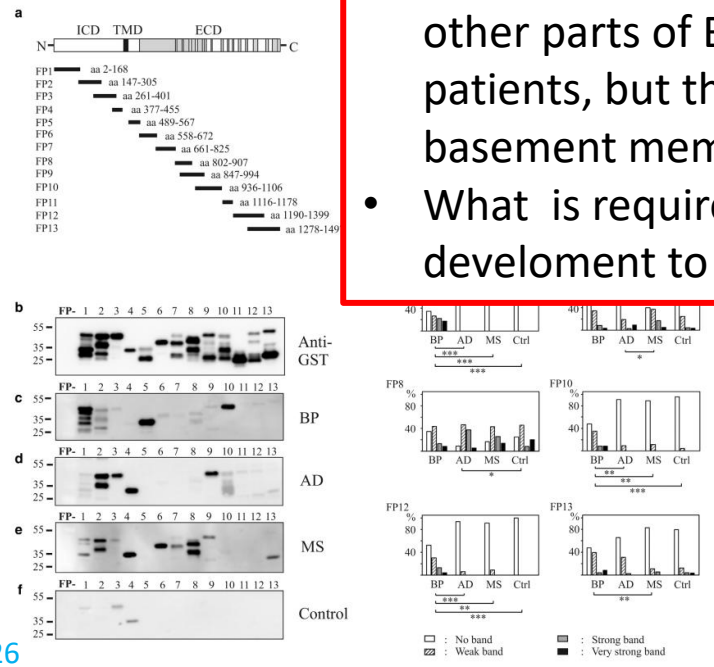
ANTIBODIES AGAINST BP180 IN PATIENTS WITH NEUROLOGICAL DISEASES

BP180 Autoantibodies Target Different Epitopes in Multiple Sclerosis or Alzheimer's Disease than in Bullous Pemphigoid

Jussi Tuusa[1], Outi Lindgren[1,2], Hanna-Mari Tertsunen[3], Wataru Nishie[4], Nina Kokkonen[1], Laura Huilaja[1], Kentaro Izumi[4], Sanna-Kaisa Herukka[3], Jouko Miettunen[5], Hiroshi Shimizu[4], Anne M. Remes[6] and Kaisa Tasanen[1]

Journal of Investigative Dermatology (2019) **139,** 293–299; doi:10.1016/j.jid.2018.09.010

- Epitope mapping showed that IgG autoantibodies of MS (n=35) and AD (n=32) patients target regions located in the intracellular and mid-extracellular parts of BP180, but not the well-known BP epitopes located in th
domain



- Autoantibodies against the NC16A domain and other parts of BP180 are found in some neurological patients, but these autoantibodies do not bind skin basement membrane
- What is required for the ”pre-clinical” state to develoment to BP ?

Received: 6 March 2024 | Revised: 24 May 2024 | Accepted: 20 June 2024
DOI: 10.1111/exd.15125

RESEARCH ARTICLE

Experimental Dermatology WILEY

Reactivity against the BP180 ectodomain in patients with bullous pemphigoid, mucous membrane pemphigoid, multiple sclerosis and Parkinson disease

Jonathan Tegtmeyer[1,2] | Maurizio Romagnuolo[1,3] | Christoph M. Hammers[1,4] | Lars Komorowski[5] | Angelo V. Marzano[3,6] |

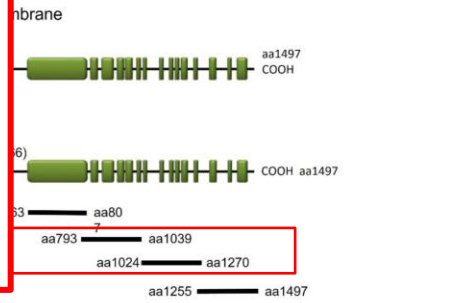


TABLE 2 Immunoblot reactivity of patients with neurological diseases against the generated recombinant fragments of the BP180 ectodomain.

	BP180(ec)1 (aa563–807)	BP180(ec)2 (aa793–1039)	BP180(ec)3 (aa1024–1270)	BP180(ec)4 (aa1255–1497)	Reactivity	Multiple reactivity
MS sera (*n*=44)	1/44 (3%)	5/44 (11%)	0/44 (0%)	3/44 (7%)	9/44 (19%)	1/75[a] (1%)
PD sera (*n*=75)	1/75 (1%)	6/75 (8%)	2/75 (3%)	7/75 (9%)	15/75(20%)	1/75[a] (1%)
Other neurological diseases sera (*n*=75)	2/75 (3%)	5/75 (7%)	0/75 (0%)	3/75 (4%)	10/75 (13%)	0/75[a] (0%)
Healthy volunteer sera, cohort B (*n*=75)	1/75 (1%)	0/75 (0%)	1/75 (1%)	3/75 (4%)	5/75 (7%)	0/75[a] (0%)

Abbreviations: aa, amino acids; MS, multiple sclerosis; PD, Parkinson disease.

MEDICATION AS A RISK FACTOR FOR BP

- Polypharmacy is common among BP patients
- Over 80 drugs have been reported to induce BP (aldosterone antagonists, loop-diuretics, spironolactone, penicillin and derivates) (Verheyden et al., 2020)
- Several case reports and registry studies have confirmed the association between BP and dipeptidyl peptidase-4 (DDP-4) inhibitors (gliptins)
- Drugs used for neurological and psychiatric conditions also increase the risk for BP
- Case reports/series which have described the association between immune checkpoint inhibitors treatment and BP

GLIPTIN-ASSOCIATED BP (GABP)

TABLE 1 | Selected case reports of gliptin-associated bullous pemphigoid.

First author	Number of cases	DPP-4 inhibitor used (n)	Latency time
Pasmatzi et al. (37)	2	Vildagliptin (2)	2 months
Skandalis et al. (38)	6	Vildagliptin (5), sitaglitpin (1)	2–13 months
Aouidad et al. (39)	3	Vildagliptin (1), sitagliptin (2)	5–6 months
Attaway et al. (40)	1	Sitagliptin (1)	12 months
Bene et al. (41)	3	Vildagliptin (3)	1–37 months
Mendonça et al. (42)	3	Vildaglitpin (2), linagliptin (1)	45 days–3 months
García et al. (43)	1	Vildagliptin	12 months
Haber et al. (44)	2	Linagliptin (2)	3–4 months
Sakai et al. (45)	1	Linagliptin (1)	9 months
Esposito et al. (46)	1	Linagliptin (1)	5 months
Yoshiji et al. (47)	5	Vildaglitpin (1), linagliptin (2), sitagliptin (1), anagliptin (1)	1–15 months
Harada et al. (48)	1	Sitagliptin (1)	3 years
Oya et al. (49)	1	Anagliptin (1)	1 month
Schaffer et al. (50)	9	Vildagliptin (4), sitagliptin (5)	5–48 months
Fania et al. (51)	5	Vildagliptin (1), sitagliptin (1), linagliptin (2), alogliptin (1)	1–8 months
Lindgren et al. (52)	10	Vildagliptin (4), sitagliptin (5), linagliptin (1)	5–24 months

Tasanen K, Varpuluoma O and Nishie W (2019) Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid. Front. Immunol. 10:1238. doi: 10.3389/fimmu.2019.01238

TABLE 2 | Epidemiological studies of gliptin-associated bullous pemphigoid.

First author	Country	Population	Cases/controls, n	Mean age (cases), y	Adjusted OR
Schaffer et al. (50)	Switzerland	Hospital data	23 (DM+BP)/170(DM)	77.6	DPP-4i: 2.49 (95% CI 0.75–8.3)
Benzaquen et al. (53)	France	Hospital data (3 hospitals)	61 (BP+DM)/122(DM)	79.1	DPP-4i: 2.64 (95% CI 1.19–5.85) Vildagliptin: 3.57(95% CI 1.07–11.84) Sitagliptin: 2.13(95% CI 0.77–5.89) Linagliptin/saxagliptin: 2.90 (95% CI 0.47–17.74)
Varpuluoma et al. (54)	Finland	Nationwide registry data	3397/12941	76.6	DPP-4i: 2.19 (95% CI 1.55–3.11) Vildagliptin: 10.4(95% CI 4.56–23.80) Sitagliptin: 1.37 (95% CI 0.93–2.01) Metformin: 1.05 (95% CI 0.88–1.24)
Kawaguchi et al. (55)	Japan	Hospital data	168 cases: DPP4i-BP 32 non-DPP4i-BP 136	79.7	NA[a]
Kridin and Bergman (56)	Israel	Hospital data	92 (BP+DM)/329 (DM)	79.1	DPP-4i: 3.16 (95% CI 1.86–5.37) Vildagliptin: 10.67 (95% CI 5.09–22.36) Linagliptin: 6.65 (95% CI 2.24–19.72) Sitagliptin: 0.42 (95% CI 0.12–1.45)
Plaquevent et al. (57)	France	Hospital data (21 hospitals). general population from reimbursement register	1787/225412	77.9	NA[b]
Lee et al. (58)	Korea	Insurance data, nationwide	670 (BP+DM)/ 670 (DM)	75.3	DPP-4i: 1.59 (95% CI 1.25–2.00) Vildagliptin: 1.91 (95% CI 1.31–2.50) Sitagliptin: 1.70 (95% CI 1.19–2.43) Linagliptin: 1.64 (95% CI 1.15–2.33) Other DPP-4is: 1.25 (95% CI 0.73–2.14)

BP, Bullous pemphigoid; CI, Confidence interval; DM, Diabetes mellitus; DPP-4i, Dipeptidyl peptidase-4 inhibitor; OR, Odds ratio.
[a]BP incidence 0.0959% of patients receiving DPP-4is.
[b]Observed frequency of DPP-4is and vildagliptin compared to general population (6.0 vs. 3.6% and 3.3 vs. 0.7%).

Do patients with gliptin-associated BP have specific clinical or immunological properties compared to "regular" BP?

BP180-NC16A autoantibodies in GABP

- 80-90 % of BP patients have IgG autoantibodies targeting the immunodominant NC16A domain of BP180

Current data suggest that the GABP patients have less NC16A IgG autoantibodies

- 30 % GABP patients were negative in the NC16A ELISA (n=108) *Plaquent et al, JID, 2018*
- Majority of GABP autoantibodies (WB) target the LABD97 autoantigen (n=18) *Mai et al, Frontiers in Immunol, 2019*
- NC16A negative autoantibodies (ELISA) are more common in GABP (35.7 %) than in regular BP (24.8 %) (n=56) *Dikmen et al, JEADV, 2022*
- NC16A negative autoantibodies (ELISA) are more common in GABP (38 %) than in regular BP (9 %) (n=60) *Salemme et al, JAAD, 2022*
- No difference in the NC16A ELISA seropositivity (n=17) *Bukvic Mokos Croat Med J, 2020*
- No difference in the NC16A seropositivity, but GABP patients had lower ELISA values *(n=24) Ständer et al, Am J Clin Derm, 2021*

Specific clinical features of GABP?

Noninflammatory subtype

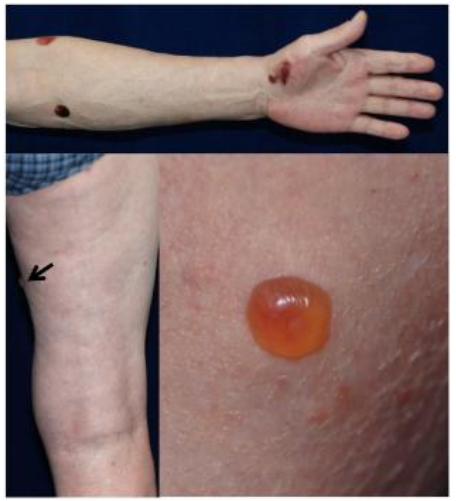
- GABP patients (n=10) have noninflammatory subtype with less erythema *Izumi et al. JID 2016*
- Noninflammatory subtype in 41 % of G-BP vs 9 % in regular BP (n=74) *Salemme et al, JAAD 2020*
- Studies not showing noninflammatory subtype in GABP *Plaquent et al, JID, 2018 (n=108); Kridin & Bergman, JAMA Derm 2018 (n=36); Lindgren et al, ACTA DV, 2019 (n=10); Bukvic Mokos Croat Med J, 2020 (n=17); Ständer et al, Am J Clin Derm, 2021 (n=24)*

Mucosal involvement

- Higher mucosal involvement in GABP (22% vs regular BP 7%, n=36) *Kridin et al, JAMA Derm, 2018*
- No difference in mucosal involvement (n=74) *Salemme et al, JAAD 2020*

Disease severity

- Severity of GABP was similar to regular BP *Plaquent et al, JID, 2018 (n=108); Kridin et al, JAMA Derm, 2018 (n=36)*
- Tendency to higher BPDAI score in GABP *Patsatsi et al, Eur J Dermatol, 2018 (n=47)*
- Higher erosion/blister BPDAI subscore (n=24) *Ständer et al, Am J Clin Derm, 2021*



Tasanen et al, Front Immunol, 2019

Type 2 Diabetes and its Treatment with Linagliptin are both Associated with Elevated Mortality in Bullous Pemphigoid

Päivi LEISTI[1#], Anna PANKAKOSKI[2#], Jari JOKELAINEN[3], Laura HUILAJA[1], Jaana PANELIUS[2], Kaisa TASANEN[1*] and Outi VARPULUOMA[1]

Published Sep 4, 2024. Acta Derm Venereol 2024; v104: 40645. DOI: 10.2340/actadv.v104.40645

- Retrospective study of 901 BP patients using electronic health record data from the Oulu and Helsinki University Hospitals: 292 had T2DM and 153 were receiving gliptins (linagliptin, sitagliptin, vildagliptin)
- Negative BP180 NC16A antibodies were more frequent in patients with GABP
- No differences in co-morbidities, the type of observed skin findings or the duration of itch
- Patients with linaglitpin treatment (n=59) for had significantly higher 5-year mortality (HR 2.1), and also the presence of T2DM not treated with gliptins was associated with elevated 5-year mortality (HR 1.5)

Table I. Characteristics of patients with bullous pemphigoid and type 2 diabetes with and without gliptin medication

	No gliptin ($n = 748$)	Gliptin ($n = 153$)	p-value
Age in years at the time of diagnosis, mean (SD)	76.4 (11.8)	78.2 (8.5)	0.07
Male sex, *n* (%)	334 (44.7)	89 (58.2)	0.003
First BP180-NC16A ELISA negative[a], *n* (%)	101 (14)	33 (22.1)	0.017
Follow-up BP180-NC16A ELISA negative[b], *n* (%)	93 (12.9)	31 (20.8)	0.017
All positive BP180-NC16A ELISA values[a], IU/mL, mean (SD)	50.3 (34.7)	51.9 (31.8)	0.63
Dementia, *n* (%)	183 (24.5)	31 (20.3)	0.313
Parkinson's disease, *n* (%)	23 (3.1)	3 (2.0)	0.628
Multiple sclerosis, *n* (%)	6 (0.8)	0 (0.0)	0.571
Any malignancy, *n* (%)	142 (19.0)	37 (24.2)	0.175
Prostate cancer, *n* (%)	32 (4.3)	10 (6.5)	0.319
Breast cancer, *n* (%)	27 (3.6)	5 (3.3)	1.000
Lung cancer, *n* (%)	4 (0.5)	0 (0.0)	0.811
Bowel cancer, *n* (%)	14 (1.9)	5 (3.3)	0.432
Non-melanoma skin cancer, *n* (%)	35 (4.7)	8 (5.2)	0.934

A Cross-Sectional Study Comparing the Prevalence of Bullous Pemphigoid Autoantibodies in 275 Cases of Type II Diabetes Mellitus Treated With or Without Dipeptidyl Peptidase-IV Inhibitors

Kentaro Izumi[1], *Wataru Nishie*[1]*, *Mutsuo Beniko*[2] and *Hiroshi Shimizu*[1]

frontiers in Immunology

ORIGINAL RESEARCH
published: 26 June 2019
doi: 10.3389/fimmu.2019.01439

TABLE 1 | Positive rates of BP180 NC16A, BP230, and BP180-FL ELISAs for each DPP-4i drug.

	BP180 NC16A	Odds ratio *p*-value	BP230	Odds ratio *p*-value	BP180-FL	Odds ratio *p*-value
DPP-4i (–) ($n = 54$)	0 (0.0%)	1.000 1.000	4 (7.4%)	1.000 1.000	3 (5.6%)	1.000 1.000
DPP-4i (+) ($n = 221$)	4 (1.8%)	1.580×10^{-7} 0.995	5 (2.2%)	0.289 0.071	24 (10.9%)	2.070 0.249
Sitagliptin ($n = 97$)	0 (0.0%)	1.000 1.000	3 (3.4%)	0.446 0.304	11 (12.6%)	2.460 0.183
Anagliptin ($n = 40$)	0 (0.0%)	1.000 1.000	0 (0.0%)	1.460×10^{-8} 0.995	2 (5.0%)	0.895 0.906
Vildagliptin ($n = 37$)	2 (5.4%)	3.610×10^{-8} 0.999	2 (5.4%)	0.714 0.707	5 (13.5%)	2.660 0.201
Teneligliptin ($n = 26$)	2 (7.7%)	5.260×10^{-8} 0.999	0 (0.0%)	1.460×10^{-8} 0.996	3 (11.5%)	2.220 0.351
Linagliptin ($n = 21$)	0 (0.0%)	1.000 1.000	0 (0.0%)	1.460×10^{-8} 0.996	3 (14.2%)	2.930 0.227
Alogliptin ($n = 9$)	0 (0.0%)	1.000 1.000	0 (0.0%)	1.460×10^{-8} 0.998	0 (0.0%)	4.000×10^{-7} 0.992
Saxagliptin ($n = 1$)	0 (0.0%)	1.000 1.000	0 (0.0%)	1.460×10^{-8} 0.999	0 (0.0%)	4.000×10^{-7} 0.997
Omaligliptin ($n = 1$)	0 (0.0%)	1.000 1.000	0 (0.0%)	1.460×10^{-8} 0.999	0 (0.0%)	4.000×10^{-7} 0.997

Use of gliptins reduces levels of SDF-1/CXCL12 in bullous pemphigoid and type 2 diabetes, but does not increase autoantibodies against BP180 in diabetic patients

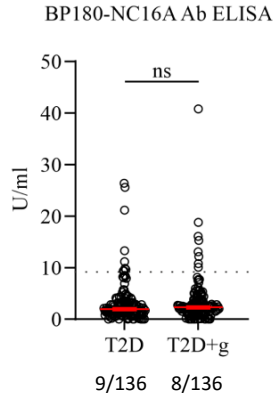
Antti Nätynki[1], Päivi Leisti[1], Jussi Tuusa[1], Outi Varpuluoma[1], Laura Huilaja[1], Kentaro Izumi[2], Sanna-Kaisa Herukka[3], Olavi Ukkola[4], Juhani Junttila[4], Nina Kokkonen[1] and Kaisa Tasanen[1]*

frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 25 July 2022
DOI 10.3389/fimmu.2022.942131

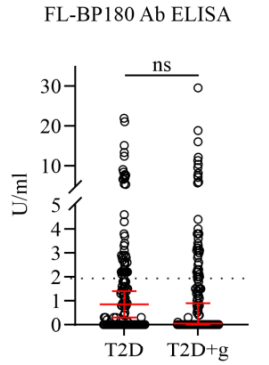
-Serum samples of T2D patients with gliptin (n=136) or without gliptin (n=136). 125 were using sitagliptin, 8 vildagliptin, 2 linagliptin, 1 saxagliptin

A



9/136 8/136

C



44/136 38/136

Dipeptidyl peptidase 4 Inhibitor–Associated Bullous Pemphigoid Is Characterized by an Altered Expression of Cytokines in the Skin

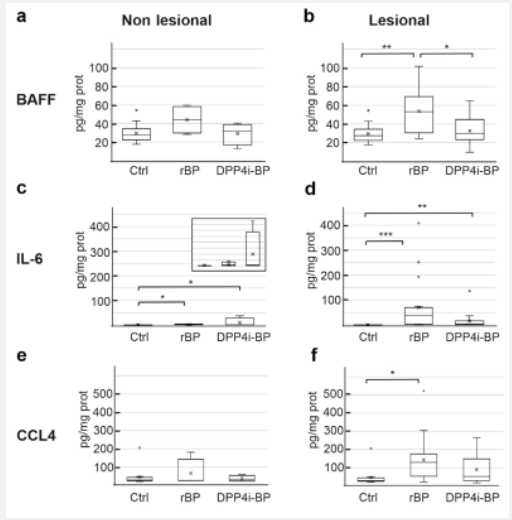
Jussi Tuusa[1,2,3], Nina Kokkonen[1,2,3], Anja Mattila[1,2,3], Laura Huilaja[1,2,3], Outi Varpuluoma[1,2,3], Sirpa Rannikko[4], Virpi Glumoff[4], Jouko Miettunen[3,5] and Kaisa Tasanen[1,2,3]

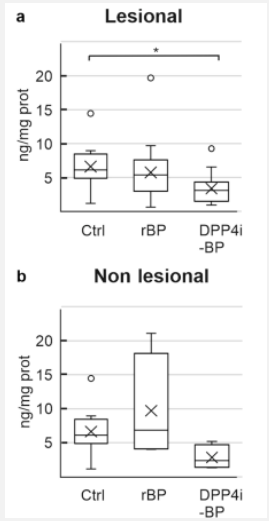
JID Open

Journal of Investigative Dermatology (2023) 143, 78–86; doi:10.1016/j.jid.2022.07.006

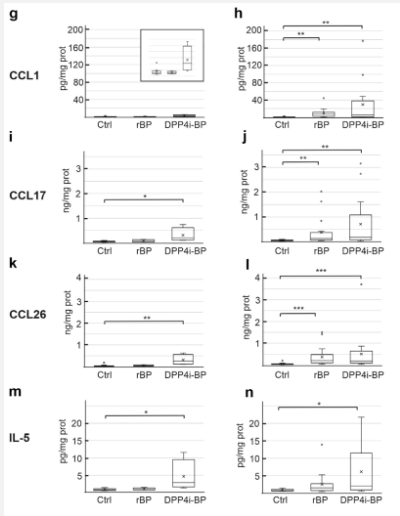
- The expression of 32 cytokines and 2 proteases were analyzed by Luminex and ELISA assays in samples from lesional and non-lesional skin of patients with regular BP (rBP, n=18/4) and GABP (=DPP4i-BP, n=17/4) and healthy controls (n=7)
- Cytokines mediating **B-cell survival and targeting such as BAFF, CCL4, IL-6 and CXCL12** (SDF-1) were expressed at higher level in the lesional regular BP skin than GABP
- GABP samples had increased levels of **eosinophilic cytokines CCL1, CCL17, CCL26 and IL-5**

→Cutaneous cytokine expression differs between patients with regular BP and GABP





CXCL12

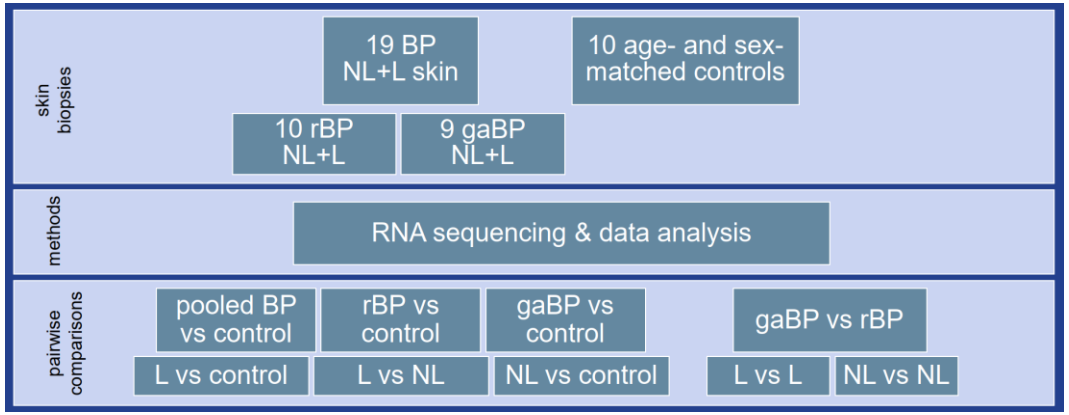


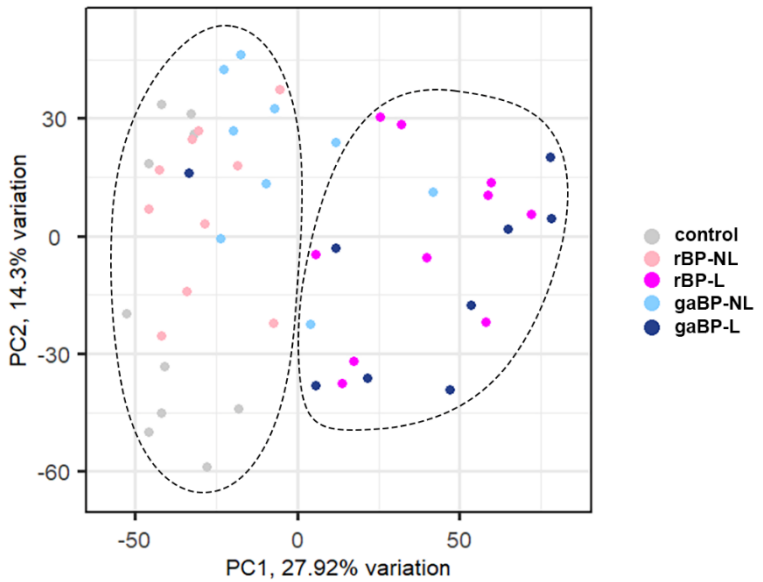
016

Identification of skin-based therapeutic targets in regular and gliptin-associated bullous pemphigoid via transcriptomics

N Kokkonen,[1,2] J Tuusa,[1,2] K Pylkäs,[2,3,4] L Huilaja[1,2] and K Tasanen[1,2] *1 Dermatology, Oulun yliopisto, Oulu, Finland, 2 Medical Research Center Oulu, Oulu, Finland, 3 Laboratory of Cancer Genetics and Tumor Biology, Oulun yliopisto, Oulu, Finland and 4 Oulu yliopisto Biocenter Oulu, Oulu, Finland*

- Analysis of cutaneous transcriptomes in gliptin-associated (GABP, n=9) and regular BP (rBP, n=10) and control samples (n=10) using RNA sequencing
- In principal component analysis transcriptomic profiles of lesional (L) skin BP samples differed from control and non-lesional (NL), but rBP and GABP lesional samples were quite similar
- Cutaneous transciptomics of rBP and GABP differ especially in non-lesional skin samples





The effect of replacement of gliptin treatment on the clinical outcome of GABP is unclear

- *Plaquent et al, JID, 2018 (n=108):* No effect to disease control and relapses whether gliptin was stopped or continued
- *Benzaquen et al, JAAD, 2018* (n=28): The clinical outcome of was worse for patients in whom gliptins were not stopped (n=19)
- *Kridin & Bergman, JAMA Derm, 2018 (n=36):* Stopping of gliptins was followed by improved clinical outcome (remission, death)

GLP-1 Analogs and SGLT2 Inhibitors Do Not Increase Risk of Bullous Pemphigoid

Journal of Investigative Dermatology (2021) **141**, 2969–2972; doi: 10.1016/j.jid.2021.05.015

Outi Varpuluoma[1,2,3], Jari Jokelainen[4,5], Laura Huilaja[1,2,3] and Kaisa Tasanen[1,2,3,]*

- A retrospective study analyse the associations between the use of oral drugs for type 2 diabetes of BP (n=5079) and BCC patients (n= 19663):

➢ GLP-1 analogs, SGLT2 inhibitors or any other type 2 diabetes drugs are not associated with increased risk of BP

→ In patients with GABP gliptins can be safely replaced with other type 2 diabetes medication

GUIDELINE

Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV)

JEADV 2022, **36**, 1689–1704

With regard to gliptins, there are conflicting results. Some open-label studies suggest the interest of stopping gliptins, but most patients received specific treatment for BP in addition to gliptin discontinuation, confounding thereby the effective beneficial impact of the gliptin withdrawal, while another large study did not show any beneficial effect of stopping the drug.[15,16] Although the effect of cessation of gliptin treatment on the clinical outcome BP remains currently unclear, a switch of the antidiabetic drug class may be considered (4.83 ± 0.47).

Solid and hematological malignancies in patients with bullous pemphigoid: A national cohort study

Outi Varpuluoma, MD, PhD,[a] Jari Jokelainen, MSc,[b] Laura Huilaja, MD, PhD,[a] and Kaisa Tasanen, MD, PhD[a]

J Am Acad Dermatol
Volume 90, Number 2

- Previous epidemiological data has not confirmed or ruled out an association between cancers and BP
- Comparision of malignancies of **3708 BP patients** using data from the Finnish Care Register for Health Care database between 1996-2018 and **14 832 controls** from the Finnish Population Registry
- The incidence of solid and hematological malignancies did not differ between BP and control population
- There was a significant association between BP and skin cancers

Table I. Incidence of malignancies in patients with BP and matched controls

	BP patients (N = 3708)	Controls (N = 14832)	OR (95% CI)
Any malignancy	1086 (29.3)	4256 (28.7)	1.03 (0.95-1.12)
Solid tumors*, excluding skin cancers	772 (20.8)	3263 (22.0)	0.93 (0.85-1.02)
Hematological malignancy	77 (2.08)	320 (2.16)	0.96 (0.75-1.24)
Skin cancers	409 (11.0)	1232 (8.31)	1.37 (1.22-1.55)
Any malignancy, nonmelanoma skin cancers excluded	804 (21.7)	3373 (22.7)	0.94 (0.86-1.03)

TREATMENT OF BP

DOI: 10.1111/jdv.18220 JEADV

GUIDELINE

Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV)

L. Borradori,[1,*] N. Van Beek,[2] C. Feliciani,[3] B. Tedbirt,[4] E. Antiga,[5] R. Bergman,[6,7] B. C. Böckle,[8] M. Caproni,[9] F. Caux,[10] N.S. Chandran,[11] G. Cianchini,[12] M. Daneshpazhooh,[13] D. De,[14] D. Didona,[15] G. M. Di Zenzo,[16] M. Dmochowski,[17] K. Drenovska,[18] J. Ehrchen,[19] M. Goebeler,[20] R. Groves,[21,22] C. Günther,[23] B. Horvath,[24] M. Hertl,[15] S. Hofmann,[25] D. Ioannides,[26] B. Itzlinger-Monshi,[27,28] J. Jedličková,[29,30] C. Kowalewski,[31] K. Kridin,[32] Y. L. Lim,[33] B. Marinovic,[34] A. V. Marzano,[34,35] J.-M. Mascaro,[36] J.M. Meijer,[24] D. Murrell,[37] K. Patsatsi,[38] C. Pincelli,[39] C. Prost,[10] K. Rappersberger,[27,28,40] M. Sárdy,[41,42] J. Setterfield,[43] M. Shahid,[44] E. Sprecher,[45] K. Tasanen,[46] S. Uzun,[47] S. Vassileva,[44] K. Vestergaard,[48] A. Vorobyev,[2,49] I. Vujic,[27,28] G. Wang,[50] K. Wozniak,[32] S. Yayli,[51] G. Zambruno,[52] D. Zillikens,[2,49] E. Schmidt,[2,53] P. Joly[4,*]

Table 3 Bullous pemphigoid (BP): therapeutic ladder, capsule summary[†]

Mild and moderate BP (BPDAI score <20 and BPDAI score ≥ 20 < 57, respectively)[‡]

- **First choice**
  - **In localized BP**, apply potent or super potent topical corticosteroids on lesions only (*may be considered*[§])
  - **In non-localized mild and moderate BP**
  - Superpotent topical corticosteroids applied twice or once a day, on whole body except the face (*is recommended*)
  - Oral corticosteroids, at an initial dose of 0.5 mg/kg/day prednisone or prednisolone (*is recommended*);
- **Second choice (may be recommended)**
  - Doxycycline
  - Dapsone

Severe BP (BPDAI score ≥ 57)

- **First choice, two treatments *are recommended***
  - Superpotent topical corticosteroids, twice or once a day, on whole body (except the face), or
  - Oral corticosteroids at an initial dose of oral prednisone 0.5 mg/kg/day
    - Note: in patients who do not achieve disease control within 1-3 weeks with 0.5 mg/kg prednisone, two options *may be considered*
      - to increase the dose of prednisone up to 0.75 mg /kg
      - to add superpotent topical corticosteroids

Corticosteroid-dependent or relapsing BP

- **Several alternative choices as adjunctive therapy *may be considered***
  - Combination with or introduction of a conventional immunosuppressive drug
    - Methotrexate
    - Azathioprine
    - Mycophenolate
- **In patients in poor general condition and/or in those with contraindications to immunosuppressive drugs, the following options *may also be considered***
  - Doxycycline
  - Dapsone
  - Omalizumab

Treatment-recalcitrant BP (resistant to 0.75 mg/kg/day of prednisone)

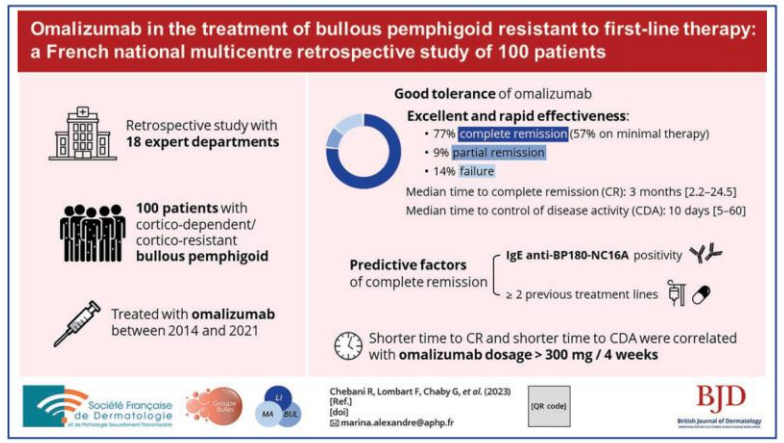
- **Combination with and/or introduction of conventional immunosuppressants *may be considered***
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
- **Other therapeutic options, which have not been validated in this setting, *may be considered* (without any prioritization)**
  - B-cell depletion therapy with anti-CD20 mAb (rituximab)
  - Omalizumab
  - Dupilumab
  - Intravenous immunoglobulins
  - Immunoadsorption

BIOLOGICS IN TREATMENT OF BP

Br J Dermatol 2024; **190**:258–266
https://doi.org/10.1093/bjd/ljad369
Advance access publication date: 4 October 2023

BJD
British Journal of Dermatology
Medical Dermatology

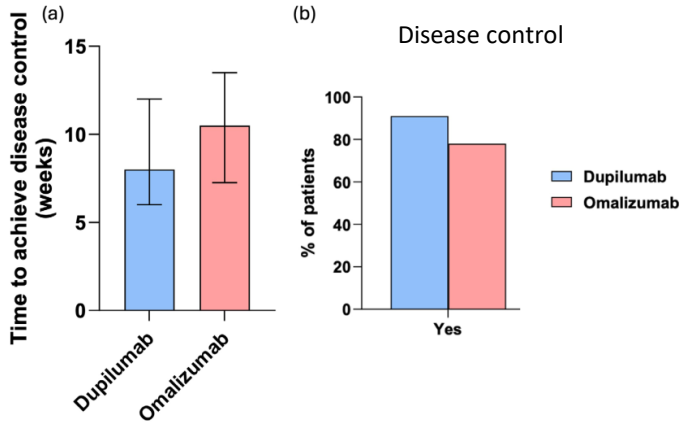
Omalizumab in the treatment of bullous pemphigoid resistant to first-line therapy: a French national multicentre retrospective study of 100 patients



Effectiveness of Dupilumab and Omalizumab in Bullous Pemphigoid: A Nationwide Retrospective Cohort Study

Gianluca Avallone[1,2] | Carlo Alberto Maronese[1,2] | Martina Zussino[1] | Simona Muratori[1] | Silvia Mariel Ferrucci[1] | Pietro Quaglino[3] | Elisabetta Manni[4] | Marco Romanelli[4] | Clara De Simone[5,6] | Caterina Foti[7] | Luigi Gargiulo[8,9] | Vincenzo Maione[10] | Piergiacomo Calzavara-Pinton[10] | Federico Bardazzi[11] | Bianca Maria Piraccini[11,12] | Emiliano Antiga[13] | Giulia Rech[14] | Riccardo Balestri[14] | Pamela Vezzoli[15] | Paolo Sena[15] | Maria Esposito[16] | Maria Concetta Fargnoli[16] | Davide Termini[1,2] | Luca Valtellini[1,2] | Rosanna Rita Satta[17] | Camilla Vassallo[18] | Alessia Provini[19] | Giovanni Di Zenzo[20] | Anna Campanati[21] | Marzia Caproni[22] | Emanuele Cozzani[23] | Simone Ribero[3] | Angelo Valerio Marzano[1,2] | DUO—DUpilumab and Omalizumab in Bullous Pemphigoid Study Group

The Journal of Dermatology, 2025; 52:983–1000
https://doi.org/10.1111/1346-8138.17742

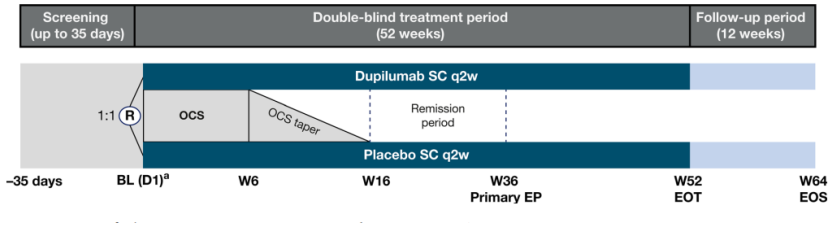


Adv Ther (2024) 41:2991–3002
https://doi.org/10.1007/s12325-024-02810-3

STUDY PROTOCOL

Study Design of a Phase 2/3 Randomized Controlled Trial of Dupilumab in Adults with Bullous Pemphigoid: LIBERTY-BP ADEPT

Dédée F. Murrell · Pascal Joly · Victoria P. Werth · Hideyuki Ujiie · Margitta Worm · Aaron R. Mangold · Elena Avetisova · Jennifer Maloney · Elizabeth Laws · Eric Mortensen · Ariane Dubost-Brama · Arsalan Shabbir



MORTALITY IN BULLOUS PEMPHIGOID

- BP is associated with an increased risk of death, the worldwide 1-year standardized mortality ratio (SMR) is 2.93 (Tedbirt et al, 2021)
- Within the first year after BP diagnosis 17-41% of patients die
- RISK FACTORS for fatal outcome: advanced age, extensive disease, type 2 DM, neurological diseases, malignancies, polypharmacy, low Karnolsky score, hypoalbuminaemia and the use high doses of systemic corticosteroids

Treatment of bullous pemphigoid with methotrexate is associated with a decreased mortality risk

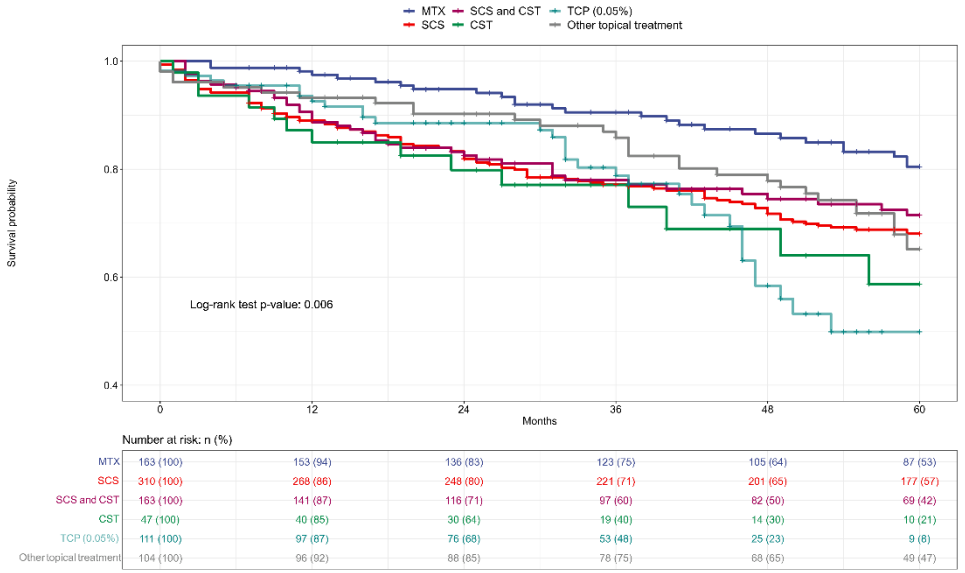
https://doi.org/10.1093/bjd/ljaf172

Päivi Leisti[1], Anna Pankakoski[2], Laura Huilaja[1], Jari Jokelainen[3], Outi Varpuluoma[1], Jaana Panelius[2] and Kaisa Tasanen[1]

BJD British Journal of Dermatology

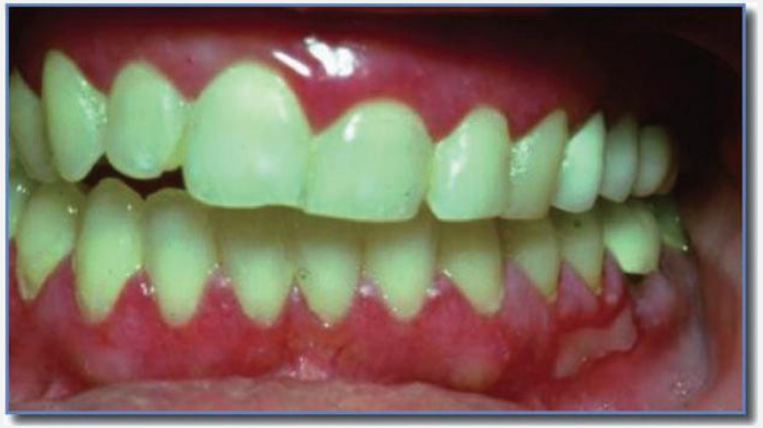
- Retrospective study of 901 BP patients using electronic health record data from the Oulu and Helsinki University Hospitals (2009-2019)
- The overall 1-year mortality rates were 8.8%, the 1-year SMR was 5.13
- Advanced age at diagnosis, concominant dementia, type 2 diabetes and a mean value of BP180-NC16A of >60 U mL predicted an increased risk of mortality
- BP patients treated with metotrexate have a significantly better prognosis than those treated with other medications

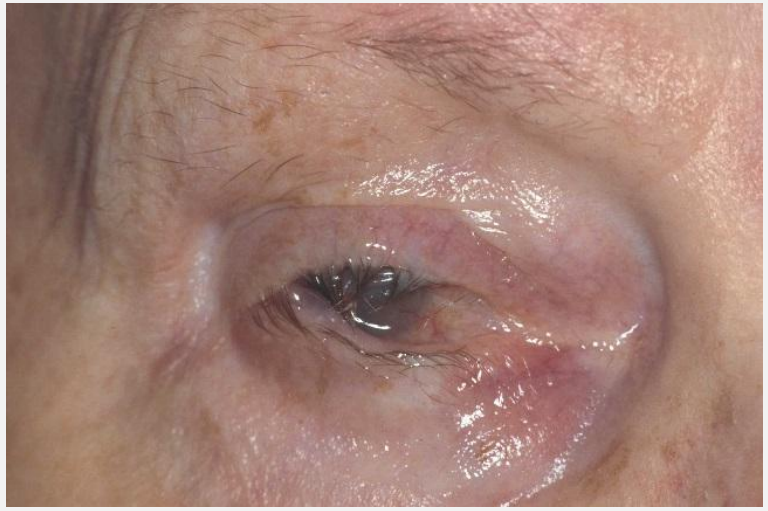
Mediation	Number of users (%)
Systemic corticosteroids	613 (68 %)
Topical corticosteroids	253 (28.5 %)
Tetracyclines	112 (12.4 %)
Metotrexate	163 (18.1 %)
Azathioprine	177 (19.6 %)
Mycophenolate	13 (1.4 %)
IVIG	5 (0.6 %)
Dapsone	27 (3 %)
Rituximab	1 (0.1 %)



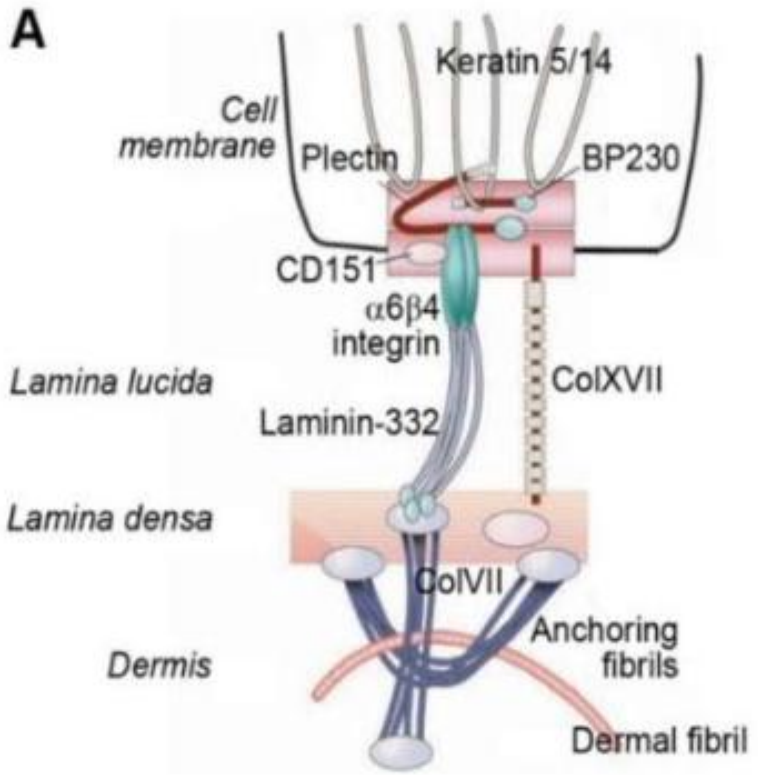
MUCOUS MEMBRANE PEMPHIGOID (MMP)

- MMP is a group of chronic and progressive sub-epidermal autoimmune bullous diseases that mainly affects mucous membranes
- MMP is typically diagnosed after 50 years of age and seems to be more common in females (2:1)
- The clinical phenotype and severity of MMP vary from mild, single site erosions to disease affecting multiple different locations and causing serious complications
- Gradual onset of symptoms
- The main affected areas are the oral mucosa (80-85 %) and conjunctiva (50 %)
- 20-25 % skin symptoms (milia, scars)





PATHOGENESIS OF MMP



- IgG and IgA autoantibodies target multiple basement membrane component including BP180/collagen XVII (75 %), laminin 332 (2-31 %), BP230 (10-28 %), α6β4 integrin (?) and collagen VII (4 %)
  - Reactivity to dermal antigens predícts more severe disease (Fairley et al, 2023)
  - 10-30 % have only IgA autoantibodies
- DIAGNOSTICS:
  - Direct IF of mucous membrane of target organ and skin (IgG, IgA, C3)
  - Indirect IF microscopy (with salt split skin)
  - ELISA, immunoblotting
  - Challenges: low titre and lower percentage of autoantibodies → Diagnostic delays usual
- Important to repeat biopsies and sera samples!

Epidemiology and Comorbidities of Mucous Membrane Pemphigoid: A National Cohort Study

Päivi Leisti[1], Laura Huilaja[1], Jari Jokelainen[2], Outi Varpuluoma[1] and Kaisa Tasanen[1,*]

Journal of Investigative Dermatology (2024) **144,** 2078–2080; doi: 10.1016/j.jid.2024.02.008

- Larger epidemiological MMP studies are rare and data on co-morbidities are contradictory
- Finnish Care Register for Health Care: 268 patients who had received a diagnosis of MMP diagnosed between 1996-2018
  - Two or more entries of ICD-10 codes L12.0 and H13.3*L12.9 and age ≥18 years
- Control group was 1072 age- and sex-matched, randomly selected individuals from the Digital and Population Data Services Agency
- The mean crude incidence rate was 2.8/million/year
- In previous studies the incidence of MMP has varied between 1.3 and 2.0/million/year (Bernard, 1995; Zillikens, 1995; Bertram 2009; van Beek 2021)

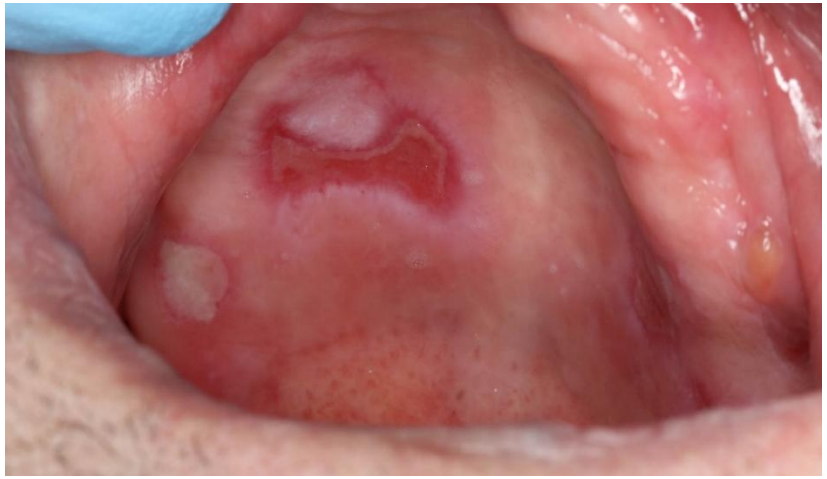
Epidemiology and Comorbidities of Mucous Membrane Pemphigoid: A National Cohort Study

Päivi Leisti[1], Laura Huilaja[1], Jari Jokelainen[2], Outi Varpuluoma[1] and Kaisa Tasanen[1,*]

Journal of Investigative Dermatology (2024) **144**, 2078–2080; doi: 10.1016/j.jid.2024.02.008

Demographic data of patients with mucous membrane pemphigoid.

	All	Female	Male
Number of cases	268 (100)	171 (63.8)	97 (36.2)
Age at diagnosis, mean (±SD)	67.3 (14.2)	66.0 (14.6)	69.5 (13.3)
Specialty of diagnosis			
Dermatology	163 (60.8)		
Dentistry	66 (24.6)		
Ophthalmology	31 (11.6)		
Other	8 (3.0)		



ASSOCIATIONS OF MMP WITH SOMATIC COMORBIDITIES

Table 1. Statistically Significant Associations of MMP with Somatic and Malignant Comorbidities

Comorbidity	n (%) MMP	n (%) Control Group	OR (95% CI)
Somatic			
Crohn's disease	6 (2.24)	4 (0.37)	6.00 (1.69–21.3)
Sjögren's syndrome	7 (2.61)	2 (0.19)	25.6 (3.13–210)
Rheumatoid arthritis[1]	19 (7.09)	20 (1.87)	4.02 (2.10–7.69)
Lichen sclerosus et atrophicus	7 (2.61)	5 (0.47)	6.49 (1.88–22.4)
Psoriasis	9 (3.36)	10 (0.93)	3.60 (1.46–8.86)
Lichen planus	31 (11.6)	5 (0.47)	30.4 (10.7–86.2)
Seborrheic dermatitis	19 (7.09)	5 (0.47)	24.3 (7.16–82.2)
Erythema multiforme	7 (2.61)	1 (0.09)	28.0 (3.44–228)
Allergic contact dermatitis	7 (2.61)	1 (0.09)	28.0 (3.44–228)
Atopic dermatitis	14 (5.22)	8 (0.75)	7.00 (2.94–16.7)
Allergic rhinitis	8 (2.99)	8 (0.75)	4.00 (1.50–10.7)
Asthma	26 (9.70)	63 (5.88)	1.70 (1.06–2.74)
Hypothyroidism	21 (7.84)	36 (3.36)	2.43 (1.40–4.24)
Type 2 diabetes mellitus	42 (15.7)	106 (9.89)	1.70 (1.15–2.50)
Essential (primary) hypertension	98 (36.6)	285 (26.6)	1.63 (1.22–2.18)
Hypertensive heart and/or renal disease	12 (4.48)	22 (2.05)	2.18 (1.08–4.41)
Atrial fibrillation and flutter	58 (21.6)	147 (13.7)	1.91 (1.31–2.78)
Atherosclerosis of arteries of extremities	17 (6.34)	38 (3.54)	1.89 (1.03–3.45)
Varicose veins of lower extremities with ulcer	6 (2.24)	6 (0.56)	4.00 (1.29–12.4)
Osteoporosis	29 (10.8)	28 (2.61)	4.89 (2.77–8.62)
Epilepsy	9 (3.36)	12 (1.12)	3.00 (1.26–7.12)
Multiple sclerosis	3 (1.12)	2 (0.19)	6.00 (1.00–35.9)
Blindness and low vision	7 (2.61)	3 (0.28)	9.33 (2.41–36.1)
Gastritis and duodenitis	23 (8.58)	42 (3.92)	2.30 (1.36–3.91)

ASSOCIATIONS OF MMP WITH MALIGNANT COMORBIDITIES

- 24.5% of anti-laminin 332 MMP patients have a malignant tumor (lung, breast, prostate, uterus, bladder) (Du et al., 2022)
- Anti-laminin 332 MMP patients have a 6.8-fold increased risk of cancer compared to the normal population (Van Beek et al, 2021)

Table 1. Statistically Significant Associations of MMP with Somatic and Malignant Comorbidities

Comorbidity	n (%) MMP	n (%) Control Group	OR (95% CI)
Malignant			
All cancers	75 (27.99)	222 (20.71)	1.55 (1.12–2.15)
Malignant neoplasm of tongue, oral cavity and pharynx	5 (1.870)	2 (0.190)	10.0 (1.94–51.5)
Malignant neoplasm of brain, meninges, spinal cord, cranial nerves, and other parts of CNS	3 (1.120)	2 (0.190)	6.00 (1.00–35.9)
Leukaemia	5 (1.870)	3 (0.280)	6.67 (1.59–27.9)
Lymphoid leukaemia	4 (1.490)	3 (0.280)	5.33 (1.19–23.8)
Skin cancers	23 (8.580)	55 (5.130)	1.73 (1.04–2.87)
Non-melanoma skin cancers	20 (7.46)	42 (3.92)	1.97 (1.14–3.41)
Squamous cell carcinoma of the skin	7 (2.610)	7 (0.650)	4.00 (1.40–11.4)

- MMP patients have more skin cancers, especially squamous cell carcinoma
- When skin cancers were excluded, no association between MMP and cancers
- No association with solid tumors

Major limitation:

- No access to electronic health records
- Laminin-332 ELISA available in Finland since 2017

→Anti-laminin 332-reactivity??

Potential correlation between anti-laminin 332 autoantibodies and malignant tumours in anti-BP180-type mucous membrane pemphigoid

Clin Exp Dermatol 2024; **00**:1–2
https://doi.org/10.1093/ced/llae124
Advance access publication date: 18 April 2024

Xiaoguang Li,[1] Hendri H Pas,[2] Hua Qian,[1] Hanan Rashid,[2] Barbara Horvath,[2] Kaan Yilmaz,[3,4] Nina van Beek,[3] Enno Schmidt,[3,5] Detlef Zillikens,[3] Norito Ishii,[6] Daisuke Tsuruta[7] and Takashi Hashimoto[7]

Table 1 Summaries of rates of coexistence of anti-laminin 332 (LM332) autoantibodies and of association with malignant tumours in anti-BP180-type mucous membrane pemphigoid (MMP) in Japan, China, the Netherlands and Germany

Different cohorts	Positive for anti-LM332 autoantibodies, % (*n*) in patients with anti-BP180-type MMP	Positive for malignant tumours, % (*n*) in patients with anti-BP180-type MMP	Anti-BP180-type MMP							
			Anti-LM332 autoantibodies (+)			Anti-LM332 autoantibodies (–)				
			Malignant tumours (+), *n*	Malignant tumours (–), *n*	Malignant tumours, %	Malignant tumours (+), *n*	Malignant tumours (–), *n*	Malignant tumours, %	Total	*P*-values[a]
Japan	28.4 (94)	9.1 (30)	11	83	11.7	19	218	8.0	331	0.29
China	47 (9)	21 (4)	1	8	11	3	7	30	19	0.31
The Netherlands	4.6 (5)	10.1 (11)	2	3	40	9	94	8.7	108	< 0.05
German	13 (8)	21 (13)	5	3	63	8	46	15	62	< 0.01
Asian (Japan + China)	29.4 (103)	9.7 (34)	12	91	11.7	22	225	8.9	350	0.43
Europe (German + the Netherlands)	7.6 (13)	14.1 (24)	7	6	53.8	17	140	10.8	170	< 0.001
Total (all four cohorts)	22.3 (116)	11.2 (58)	19	97	16.4	39	365	9.7	520	< 0.05

- European MMP patients have significantly lower frequency for positive anti-laminin 332 autoantibodies than Asian patients (7.6 % vs. 29.4 %)
  - Use of different methods to detect anti-laminin 322 autoantibodies
- Positive correlation between anti-laminin 332 autoantibodies and malignant tumours in European (the Dutch and German) MMP patients

SUMMARY

- BP, MMP and DH are the most common AIBDs in Finland
- Neurodegenerative diseases and gliptins increase significantly the risk for subsequent BP, mechanisms??
- GABP seems to have some particular clinical and immunological properties
- Although the development of new therapeutics has been challenging, the treatment of BP is shifting towards the use of biologics
  - Dubilumab, omalizumab, nemolizumab, JAK inhibitors, FcRN inhibitors (ergartigimod)
- More data is needed to evaluate if treatment with methotrexate indeed reduces the risk of death in BP
- MMP: slow disease course, low antibody levels, multiple antigens →diagnostic delays
- Patients with anti-laminin 332 MMP have an increased risk for malignancies

Thank you for your attention!

Research group in Oulu:
- Anna-Kaisa Försti
- Laura Huilaja
- Nina Kokkonen
- Päivi Leisti
- Outi Lindgren
- Antti Nätynki
- Outi Varpuluoma
- Emilia Veikkolainen
- Jussi Tuusa

Collaborators:
- Oulu: Jari Jokelainen, Markku Timonen, Johannes Kettunen, Eeva Sliz
- Tampere, Finland: Teea Salmi, Kaisa Hervonen, Katri Kaukinen
- Helsinki, Finland: Anna Pankakoski, Jaana Panelius, Katariina Hannula-Jouppi
- Sapporo/Hakodate, Japan: Wataru Nishie, Kentaro Izumi

ACADEMY OF FINLAND

JUSELIUS SIGRID STIFTELSE

UNIVERSITY OF OULU

15.1 MRC OULU medical research center

OYS OULU UNIVERSITY HOSPITAL