diagnosed as anti-p200/lamγ1 pemphigoid. In addition, 13 sera (9.2%) contained AAbs exclusively reactive with Col7, and 4 (2.8%) contained AAbs exclusively reactive with lam332. In 9 of the cohort of 141 sera (6.4%), no target antigen was identified (Fig 2).

In summary, anti-p200/lamγ1 pemphigoid was by far the most frequent pemphigoid disease, with 78.7% of the 141 patients having dermal binding AAbs, followed by EBA in 11.4% of patients and anti-lam332 MMP in 3.5% of patients.

Dual reactivity with different antigens may be explained either by cross-reactive AAbs or by epitope spreading, which is a phenomenon that describes the generation of AAbs with different antigen specificities in the same patient.[1] Our data suggest that epitope spreading may occur more frequently in anti-p200/lamγ1 pemphigoid than in EBA and anti-lam332 MMP.

Imke Lau,[a] Stephanie Goletz, PhD,[a] Maike M. Holtsche, MD,[a] Detlef Zillikens, MD,[b] Kai Fechner, Ing,[c] and Enno Schmidt, MD, PhD[a,b]

From the Lübeck Institute for Experimental Dermatology[a] and Department of Dermatology, University of Lübeck, Lübeck, Germany,[b] and Institute of Experimental Immunology, EUROIMMUN AG, Lübeck, Germany[c]

Authors Lau and Goletz contributed equally to this work.

Funding sources: Supported by structural funding from the Schleswig-Holstein Cluster of Excellence Inflammation at Interfaces (DFG EXC306/2) and the CRU 303 Pemphigoid Diseases.

Disclosure: Mr Fechner is an employee of EUROIMMUN. Dr Schmidt and Dr Zilliken have a scientific cooperation with EUROIMMUN. Ms Lau, Dr Goletz, and Dr Holtsche have no conflicts of interest to disclose.

Reprints not available from the authors.

Correspondence to: Enno Schmidt, MD, PhD, Department of Dermatology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

E-mail: enno.schmidt@uksh.de

REFERENCES

1. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;381:320-332.
2. Ghohestani RF, Nicolas JF, Rousselle P, et al. Diagnostic value of indirect immunofluorescence on sodium chloride-split skin in differential diagnosis of subepidermal autoimmune bullous dermatoses. *Arch Dermatol*. 1997;133:1102-1107.
3. Goletz S, Hashimoto T, Zillikens D, et al. Anti-p200 pemphigoid. *J Am Acad Dermatol*. 2014;71:185-191.
4. Goletz S, Probst C, Komorowski L, et al. Sensitive and specific assay for the serological diagnosis of anti-laminin 332 mucous membrane pemphigoid. *Br J Dermatol*. 2019;180(1):149-156.
5. Komorowski L, Muller R, Vorobyev A, et al. Sensitive and specific assays for routine serological diagnosis of epidermolysis bullosa acquisita. *J Am Acad Dermatol*. 2012;68:e89-e95.

https://doi.org/10.1016/j.jaad.2019.03.077

Methodologic gaps and risk of bias in randomized controlled trials of local anogenital wart treatments

To the Editor: The latest guidelines for first-line treatment of anogenital warts (AGWs) in immunocompetent adults failed to establish a therapeutic hierarchy[1,2] because of methodologic gaps in research and insufficient randomized controlled trial (RCT) evidence. This section of our systematic review (Prospero no. CRD42015025827) addresses these insufficiencies and provides recommendations for future RCTs of AGW treatments.

A search was conducted through 12 databases from their inception to August 1, 2018 (supplemental material available at https://www.mendeley.com/community/journal-of-the-american-academy-of-dermatology/). RCTs were included when a provider- or patient-administered treatment was reported in ≥1 parallel treatment group; the other inclusion criteria were reported in a previous paper.[3] The primary outcomes were percentage of clearance and percentage of recurrence, and the Cochrane Collaboration risk of bias tool and its methodology[4] were used.

In total, 70 unique RCTs involving 9931 individual patients (mean 142 participants/study) fulfilled the inclusion criteria (Appendix S2). The overwhelming majority of included RCTs (66/70) were found to be of poor quality (Appendix S3). A risk of performance bias due to knowledge of the allocated intervention by participants and personnel (excluding outcome assessor) was detected in 31 of 70 RCTs (row 3, Appendix S3). The risk of detection bias due to knowledge of the allocated intervention by outcome assessors was high in 10 of 70 and unclear in 35 of 70 RCTs (row 4, Appendix S3). The risk of selection bias due to inadequate generation of a randomized sequence was high in 7 of 70 and unclear in 38 of 70 RCTs (row 1, Appendix S3). Other biases corresponded mainly to pharmaceutical funding or to conflicts of interest; the risk was high in 25 of 70 RCTs and unclear in 35 of 70 RCTs (row 7,

Appendix S3). A selection bias was suspected in many RCTs (57/70) (row 2, Appendix S3). High risk of attrition bias and reporting bias was evident in 19 of 70 and 20 of 70 RCTs, respectively (rows 5 and 6, Appendix S3). Thirty-five RCTs were published since the first CONSORT (Consolidated Standards of Reporting Trials) statement was released (1996)[5]; among these, 12 had a high or uncertain risk of reporting bias. AGW clearance was assessed from immediately after treatment (mainly for provider-administered therapies) up to 4 months later, depending on the study. Recurrence was occasionally assessed (15/70 RCTs) 1-12 months after clearance.

The following should be considered in future RCTs. Participants and physicians should be systematically blinded to the allocated intervention, and both AGW clearance and recurrence should be assessed at fixed time points (a consensus is lacking on this point) by an independent expert unaware of the allocated intervention. Proper randomization procedures should be strictly followed. The CONSORT statement must imperatively be employed. Systematic information on previous therapies and on AGW location and characteristics should be provided to enable efficacy analyses. The unit of analysis must always be the patient, as the primary goal is full recovery. Split studies should be avoided for statistical reasons but also because of the risk of performance bias. In future RCTs, the percentage of AGW recurrence, which is an important yet often neglected outcome, should also be evaluated. Nevertheless, RCT assessment of recurrence raises important methodologic problems, including a high rate of loss to follow-up and recontamination.

We would like to thank Prof Rodolphe Thiebaut for his continuous support, our research librarian Evelyne Mouillet, the dermatologists of the French Group of Dermato-Infectiology and Sexually Transmitted Diseases of the Société Française de Dermatologie and the Association des Dermatologues des Alpes du Sud, and our copy editor Arianne Dorval.

Antoine Bertolotti, MD,[a,b] Brigitte Milpied, MD,[c] Sébastien Fouéré, MD,[d] André Cabié, MD, PhD,[b,e] Nicolas Dupin, MD, PhD,[f] and Christian Derancourt, MD[b,g]

From the Department of Infectious Diseases, Reunion University Hospital, Saint-Pierre, La Réunion, France[a]; EA 4537, Antilles University, Martinique, France[b]; Department of Dermatology and Pediatric Dermatology, National Center for Rare Skin Disorders, Saint-André and Pellegrin Hospitals, Bordeaux, France[c]; Department of Dermatology, Saint-Louis Hospital, Paris Diderot University, Paris, France[d]; Department of Infectious Diseases, Martinique University Hospital, Fort-de-France, Martinique, France[e]; Department of Dermatology, Cochin Hospital, Paris Descartes University, Paris, France[f]; and DRCI, Martinique University Hospital, Fort-de-France, Martinique, France[g]

Funding sources: Supported by grants from the Allocation Jeunes Chercheurs Hospitaliers 2015 and the Programme Hospitalier de Recherche Clinique Interrégional (no. 13 069).

Conflicts of interest: None disclosed.

Reprint requests: Antoine Bertolotti, MD, Department of Infectious Diseases, CHU de la Réunion, Saint-Pierre, La Réunion, France

E-mail: antoine_bertolotti@yahoo.fr

REFERENCES

1. Lacey CJN, Woodhall SC, Wikstrom A, et al. 2012 European guideline for the management of anogenital warts. *J Eur Acad Dermatol Venereol*. 2013;27(3):263-270.
2. Anogenital warts - 2015 STD treatment guidelines. https://www.cdc.gov/std/tg2015/warts.htm. Accessed July 17, 2017.
3. Bertolotti A, Dupin N, Bouscarat F, et al. Cryotherapy to treat anogenital warts in nonimmunocompromised adults: systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77(3):518-526.
4. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
5. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA*. 1996;276:637-639.

https://doi.org/10.1016/j.jaad.2019.03.080

Association between prurigo nodularis and malignancy in middle-aged adults

To the Editor: Prurigo nodularis (PN) is an extremely pruritic, inflammatory skin disease associated with multiple underlying comorbidities.[1] Case reports have noted an association between PN and malignancies, including lymphoma[2,3] and solid organ tumors.[4] The goal of this cross-sectional study was to evaluate an association between PN and a variety of malignancies in a diverse patient population.

Institutional review board approval was waived for this study because only anonymous aggregate-level data were used. The study population consisted of 695 patients aged 40-69 years who presented to the Johns Hopkins Health System during 2013-2017