improve beyond week 24. Limitations of the study include a slower-than-expected enrolment – possibly because ADA monotherapy was the preferred approach of Canadian dermatologists to treat psoriasis – and the single-arm study design as each participant served as their own control, and outcomes after addition of MTX are compared with similar assessments at baseline. The variability in MTX dosing based on investigator judgement may have been another limitation.

In a real-world setting over 24 weeks, adding MTX to ADA increased treatment satisfaction, effectiveness and quality of life in patients with psoriasis suboptimally responding to ADA monotherapy. No new safety signals were detected.

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Conflicts of interest: see Appendix S1S1 for full statement.

Data availability: AbbVie is committed to being transparent regarding the clinical trials sponsored by sharing data from and information about clinical trials (https://vivli.org/).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full conflicts of interest statement.

Bullous pemphigoid after SARS-CoV-2 vaccination: spike-protein-directed immunofluorescence confocal microscopy and T-cell-receptor studies

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Dear Editor, Growing evidence suggests that SARS-CoV-2 vaccination is associated with a variety of cutaneous reactions. These include autoimmune-mediated conditions such as autoimmune blistering diseases (AIBDs), one of which is bullous pemphigoid (BP).[1,2] We report new-onset BP in two patients following their first SARS-CoV-2 vaccination.

The first patient was an 80-year-old man who noticed reddish itchy macules with small blisters on his lower legs 1 week after vaccination with BTN162b2.[2] Two weeks later, after he had received his second shot, these erythematous/bullous lesions spread over his trunk (Figure 1a). The second patient was an 89-year-old man who noticed 2 days after the first BTN162b2 vaccination itchy erythematous/bullous lesions on his entire integument. Neither of the patients reported intake of any new medications or other newly diagnosed conditions prior to the AIBDs.

In both cases, subepidermal clefts were demonstrated on routine histology (Figure 1b). In both patients, direct immunofluorescence on frozen sections revealed linear deposits of IgG and C3 at the basement membrane zone. Indirect immunofluorescence showed bandlike IgG deposits on the epidermal side in both patients. In both cases, enzyme-linked immunosorbent assay revealed highly elevated autoantibody levels against BP-180 (365 U mL^{-1} and 115 U mL^{-1}, normal

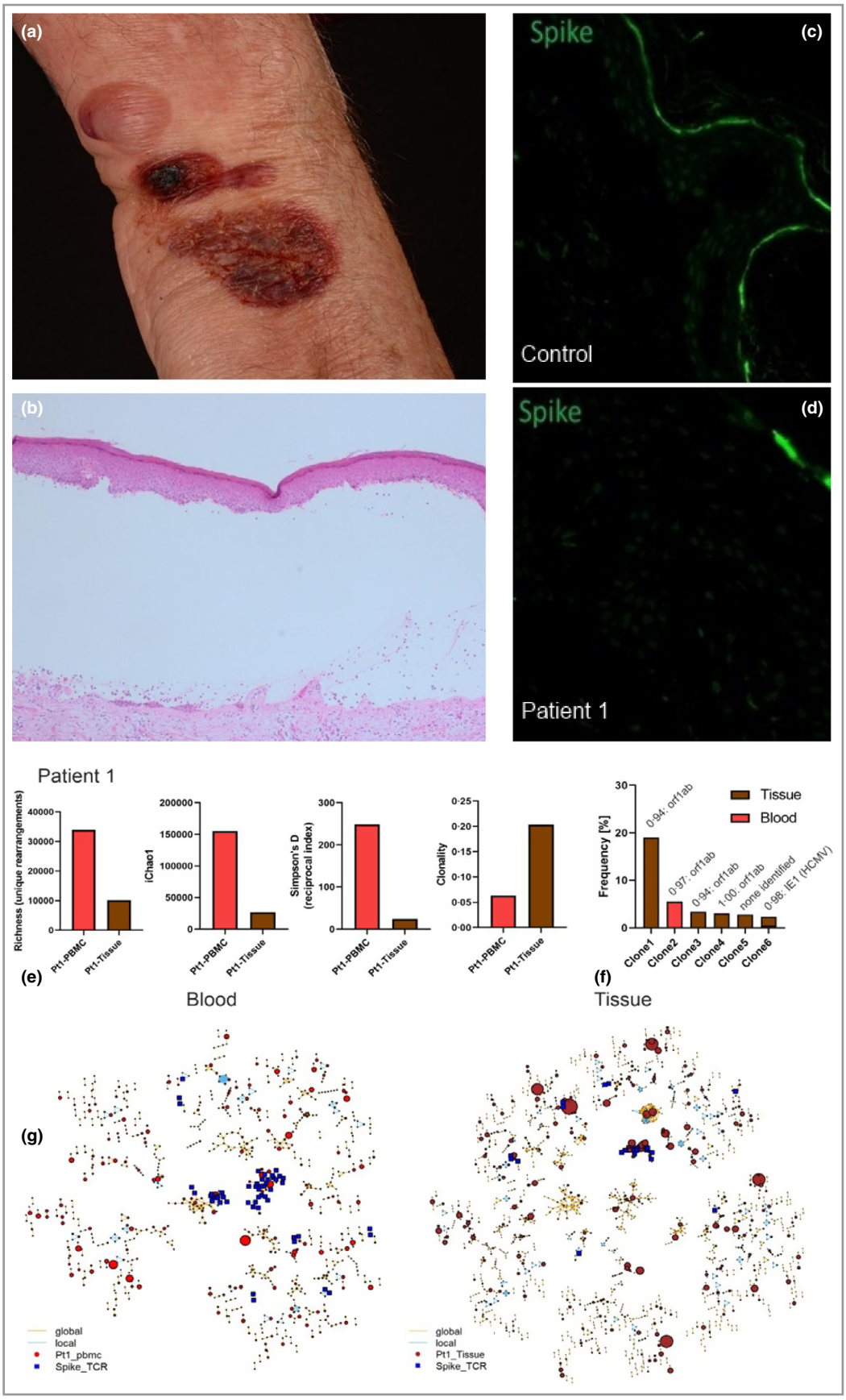

Figure 1 (a) Clinical presentation of COVID-19 vaccine-induced bullous pemphigoid in the first patient. (b) On haematoxylin–eosin histology, both patients displayed slight spongiosis and subepidermal blisters with lymphocytic and eosinophilic infiltrates. (c, d) Representative immunofluorescence confocal microscopy images of normal skin of a control patient (c) and lesional skin of patient 1 (d) showing spike protein immunoreactivity. However, there was only a very likely unspecific immunoreactivity in the horny layer of the patient and control skin. (e) T-cell receptor (TCR) analysis of patient 1. Classical TCR repertoire metrics: richness gives the number of unique TCR rearrangements within a sample; iChao1 is an estimator of the lower bound of the true richness of a sample; Simpsons' diversity reflects the probability that two randomly picked sequences from a sample are the same; clonality reflects the abundance of clonally expanded T-cell clonotypes within a sample. PBMC, peripheral blood mononuclear cell. (f) Frequency of the top six expanded T-cell clonotypes within the whole TCR repertoire including blood and tissue of a patient. TCRMatch was used to infer the antigen specificity of the respective clonotype. (g) Clonotypes were annotated with the antigen specificity with the highest score according to TCRMatch. Depiction of the results from application of the GLIPH algorithm. Global similarities are marked in orange and local similarities in blue. Additional TCR sequences that recognize the SARS-CoV-2 spike protein (VDJdb) were subjoined to infer antigen specificity.

range < 20) and BP-230 (223 U mL^{-1} and 41 U mL^{-1}, normal range < 20). Hence, both patients were diagnosed with BP. Both were successfully treated with a tapered systemic prednisolone regimen.

For immunofluorescence confocal laser scanning microscopy imaging, we used the antibody SARS-CoV/SARS-CoV-2 Spike Protein S2 [mouse/IgG1, monoclonal antibody (clone 1A9), catalogue no. MA5-35946 (Thermo Fisher Scientific, Waltham, MA, USA)]. We did not observe immunoreactivity for SARS-CoV-2 spike protein in the subepidermal compartment. There was only a very likely unspecific immunoreactivity in the horny layer of the patient and control skin specimens (Figure 1c, d). High-throughput sequencing of the T-cell receptor (TCR)Vβ CDR3 and TCR repertoire was investigated in lesional skin tissue and isolated peripheral blood mononuclear cells. Within the lesions of both patients, we observed a high clonality of T cells, with the top expanded T-cell clone contributing almost 20% of all TCR transcripts (Figure 1e).

Using TCRMatch[3] to estimate the antigen specificity of the expanded T-cell clonotype we found that several of the expanded T-cell clones were indeed reactive to SARS-CoV-2 (Figure 1f). Using the GLIPH algorithm,[4] we identified several TCR clusters derived from T cells in both lesional tissue and peripheral blood that co-clustered with the added spike-protein-reactive TCRs (Figure 1g). Importantly, by contrast, in control tissues obtained prior to the COVID-19 pandemic or SARS-CoV-2 vaccinations, SARS-CoV-2 spike-protein-reactive T cells were not observed (data not shown).

The similarities with respect to both timing and the clinical and molecular features in the cases presented here point to a causal relationship between the vaccination and BP. There are several published cases of vaccine-induced BP, the majority involving influenza but more recently also COVID-19.[1,5,6] For SARS-CoV-2 vaccines, the target antigen is the surface spike protein, which is used by the virus to bind and fuse with host cells. When speculating on autoimmune mechanisms following SARS-CoV-2 infection one may particularly consider molecular mimicry.[7,8] We hypothesized that molecular mimicry may exist between basement-membrane-specific proteins (e.g. BP-180, BP-230) and the SARS-CoV-2 spike protein. However, using an antibody against the spike protein we could not confirm this hypothesis.

With respect to the TCR repertoire in lesional skin, we observed a marked clonal expansion of T cells in both patients with BP, indicating an ongoing adaptive immune response. However, we cannot exclude that this T-cell expansion was an epiphenomenon due to the vaccination per se. The two bioinformatic approaches further suggested that these T-cell responses were reactive to SARS-CoV-2-derived epitopes.[3,4] Our TCRMatch results suggested that some of the expanded T-cell clones detected in the patients might be reactive to other SARS-CoV-2-derived epitopes including nucleocapsid proteins. However, whether these T-cell clones might hint at an undocumented previous infection with SARS-CoV2 or some other mechanism, whereby a spike protein vaccine may induce such T cells, remains unclear at this point.

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Telehealth for older adults with skin disease: a qualitative exploration of dermatologists' experiences and recommendations for improving care

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Dear Editor, The COVID-19 pandemic has accelerated the use of telehealth, defined as the delivery of healthcare via remote technologies,[1] with widespread adoption of live-interactive video visits across the USA.[2–4] Yet, it is important to avoid exacerbating healthcare disparities for vulnerable populations such as older adults, who traditionally have more technological literacy barriers.[5,6] Our aim was to explore dermatologists' experiences of using telehealth with older adults, in order to identify and summarize recommendations to improve telehealth care.

Author I.d.V.H. conducted 23 in-depth, semistructured interviews (February to August 2021) over video with dermatologists who had self-reported experience of caring for adults age > 65 years using telehealth. We conducted an inductive thematic analysis of the full interview transcripts, using a constant comparison and mind-mapping approach.[7] This study was approved by the Stanford Institutional Review Board.

Of the 23 dermatologists interviewed, 13 were female and 10 were male, with 14 attendings and nine residents from eight different states. Seven participants identified as Asian, four as black or African American and 12 as white. Every dermatologist interviewed for this study thought that telehealth 'is here to stay'. The following core themes regarding dermatologists' experience (E1–E5) of telehealth use with older adults were extracted.

E1. *Perceived benefits of telehealth for older adults*. The perceived benefits of patients being able to stay in their own home for an appointment stretched beyond the context of the pandemic. Examples cited included the reduction in travel time and associated expense, which could be particularly pertinent to older adults with transport limitations, need for assistance from caregivers or mobility issues. E2. *Works well for 'stable chronic disease', but concerns about diagnosis of malignant lesions*. An inability to perform biopsies or whole-skin exams often made evaluation of potential neoplastic lesions challenging via telehealth. In contrast, situations in which the dermatologist was not dependent on virtual image quality, but rather the subjective patient report, were emphasized as well suited to virtual visits. E3. *Technology presents a barrier for many, but not all, older adults*. There was considerable variation in experiences, with many examples of issues with technological difficulties arising, although some providers reported being 'impressed and surprised' with how older adults adapted to telehealth. E4. *Can't see the whole patient and feel the skin*. Practical issues that limit patient examination and procedures were cited as limitations of telehealth and reasons for transition to in-person care. E5. *Can be more difficult to communicate virtually*. This theme encompasses both personal connection and rapport, and practical communication issues such as 'if the patient speaks a different language', with access to an interpreter being complicated via telehealth.

Five themes summarizing recommendations (R1–R5) for use of telehealth with older adults were identified. R1. *Give comprehensive instructions ahead of time*. This included requests for high-quality photos (and guidelines on how to take them) irrespective of access to video in the telehealth visit, as well as detailed login instructions. R2. *Appropriate appointment triage is crucial*. Interviewees differed in their opinions regarding how this triage should manifest; some expressed a preference 'to see all new patients in person', while others found telehealth visits an effective adjunct to triage in itself. Frustrations around failure of effective triage for both patient and provider were cited. R3. *Don't make assumptions about patient comfort with technology*. Although there were many accounts of technological issues arising with elderly patients, many of the providers' preconceptions about older adults' ability to use telehealth were not borne out in practice. R4. *Important to manage patient expectations about what can be achieved in a telehealth visit*. The importance of patient education regarding what can be achieved in a telehealth visit was emphasized: 'the patient's perception was suddenly [that] we could take care of things on the computer and they didn't have to come in, which of course turns out not to be true'. R5. *Need to make telehealth accessible for all*. There is a potential paradox to telehealth access: although telehealth offers tremendous capacity to improve healthcare access, those who might benefit most are often least well equipped to access the technology required. Some participants felt optimistic about the ability of the future telehealth landscape to increase