Table 1 Cases of pyoderma gangrenosum (PG) with concomitant viral hepatitis ranked by fulfilment of diagnostic criteria in ascending order[a]

Author	Virus	Use of diagnostic criteria (yes/no)	Cryo	Su *et al.*, major (2/2)	Su *et al.*, minor (2/4)	Maverakis *et al.*, major (1/1)	Maverakis *et al.*, minor (4/8)	Combined score (/15)	Fulfils Maverakis *et al.*	Fulfils Su *et al.*	Fulfils both
Wang *et al.*	HBV	No	NR	2	4	1	7	14	Yes	Yes	Yes
Ahmad *et al.*	HCV	No	No	2	3	1	6	12	Yes	Yes	Yes
Smith *et al.*	HCV	No	Yes	2	2	1	4	9	Yes	Yes	Yes
Pourmorteza *et al.*	HCV	No	Yes	0	0	0	0	9	Yes	No	No
Yurci *et al.*	HCV	No	No	2	2	1	3	8	No	Yes	No
Iardino *et al.*	HCV	No	No	0	0	0	0	7	No	No	No
Keane *et al.*	HCV	No	NR	1	1	0	4	6	No	No	No
Hamzi *et al.*	HCV	No	NR	0	0	0	0	6	No	No	No
Bekkal *et al.*	HCV	No	No	0	0	0	0	5	No	No	No
Kondo *et al.*	HCV	No	Yes	0	0	0	0	4	No	No	No

Cryo, cryoglobulinemia; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported. [a]Scoring of included cases of viral PG based on diagnostic criteria domains from Su *et al.*[2] and Maverakis *et al.*[3] Cryoglobulinemia is also noted – two of the three most compelling cases of PG with HCV have an associated cryoglobulin. References for the included studies are available from the authors on request.

if detected, additional causes should be investigated, including HCV and plasma cell dyscrasias.

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COVID-19 outcomes in patients with autoimmune blistering disease

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Dear Editor, Autoimmune blistering diseases (AIBD) are often treated with immunosuppressive medications, including rituximab, yet the implications of these approaches during the COVID-19 pandemic are not fully understood.

COVID-19 outcome studies in patients with AIBD are limited by small sample sizes and interpretation complicated by advanced age and comorbidities common in this population. On the one hand, although a diagnosis of bullous pemphigoid (BP) alone may present a higher risk of death from COVID-19

disease,[1] a review of published case reports[2] and a population-based cohort study[1] of patients with AIBD who had confirmed SARS-CoV-2 infection (16 and 36 patients, respectively), suggested that immunomodulatory treatments do not increase risks of contracting COVID-19 or of poor outcomes. On the other hand, a study of 17 patients with AIBD who had documented SARS-CoV-2 infection found increased risk of hospitalization with more recent rituximab treatment,[3] suggesting that the risks of treatment, especially with rituximab, deserve further investigation. Indeed, an increased risk of death has been observed among rheumatology patients on rituximab.[4–6]

To provide clarity on the risk of treating AIBD with immunosuppressive therapies, particularly rituximab, during the pandemic, we assembled and analysed outcomes in a cohort treated in our US institution. We performed an institutional review board-approved retrospective search of the electronic health record for patients with diagnoses of pemphigoid or pemphigus and conducted a chart review of those who had SARS-CoV-2 infection confirmed by polymerase chain reaction between 1 February 2020 and 1 July 2020. Additionally, we contacted patients with AIBD followed in our academic tertiary care clinic and reviewed the history of those diagnosed with COVID-19. Of 19 patients with AIBD identified, 11 patients had BP, one had ocular cicatricial pemphigoid, four had pemphigus vulgaris (PV), and three had pemphigus foliaceus. Clinical findings are summarized in Table 1.

In our cohort, the only patients who succumbed to COVID-19 were treated with rituximab. Although three patients who received rituximab $\geq$ 6 months prior recovered without intervention, two of three who received rituximab $\leq$ 5 months prior to COVID-19 diagnosis died. One was a 74-year-old man with PV and hypertension on prednisone 40 mg daily who received rituximab 2 months prior to COVID-19 diagnosis; he was treated with remdesivir, convalescent plasma and mechanical ventilation. The other was an 82-year-old woman with BP, dementia, chronic obstructive lung disease and hypertension, all of which are independent risk factors for poor outcome, who received rituximab 4 months prior to

Table 1 Characteristics and COVID-19 outcomes of patients with autoimmune blistering diseases (AIBD) who contracted COVID-19

AIBD	Treatment	Age, years	Sex	Comorbidities	Hospitalized?	Outcome
BP	RTX – 4 months prior	82	F	Dementia, stroke, COPD, Parkinson's disease, hypertension, hyperlipidaemia	No[a]	Deceased
PV	RTX – 2 months prior, pred 40 mg	74	M	Hypertension	Yes[b]	Deceased
PV	RTX – 5 months prior, MMF	65	M	Obesity	No[c]	Recovered
PV	RTX – 6 months prior, MMF	52	F	Diabetes, hypertension	No	Recovered
PV	RTX – 34 months prior	60	F	Hypertension, pneumonia, lung nodules	No	Recovered
PF	RTX – 33 months prior	38	M		No	Recovered
BP	MMF	65	M	Renal failure, heart failure, diabetes, hypertension, obesity	No	Recovered
BP	MMF, pred 5 mg	75	F	COPD, smoking, pulmonary nodule	Yes[d]	Recovered
PF	MMF	67	M	Stroke, diabetes, hyperlipidaemia, smoking history	Yes[e]	Recovered
BP	MTX, pred 40 mg	59	M	Diabetes, coronary artery disease, hypertension, hyperlipidaemia	No	Recovered
BP	MTX, pred 5 mg	70	M	Diabetes	No	Recovered
BP	MTX	80	F	Dementia, stroke, rheumatoid arthritis	No	Recovered
BP	MTX	75	F	Hypertension, chronic renal disease, obesity, hyperlipidaemia	No	Recovered
OCP	MTX	91	F	Parkinson's disease, hyperlipidaemia	No	Recovered
BP	DCN	99	F	Dementia, hypertension, hyperlipidaemia, chronic renal disease	Yes[f]	Recovered
PF	DCN, TCS	74	M	Cerebral palsy, diabetes, hypertension, stroke	No	Recovered
BP	MCN	90	F	Diabetes, coronary artery disease, hypertension, hyperlipidaemia	No	Recovered
BP	TCS	88	F	Dementia, hypertension, heart failure	No	Recovered
BP	TCS	102	F	Hypertension, pulmonary embolism	Yes[g]	Recovered

BP, bullous pemphigoid; COPD, chronic obstructive pulmonary disease; DCN, doxycycline; F, female; M, male; MCN, minocycline; MMF, mycophenolate mofetil; MTX, methotrexate; OCP, ocular cicatricial pemphigoid; PF, pemphigus foliaceous; pred, prednisone; PV, pemphigus vulgaris; RTX, rituximab; TCS, topical corticosteroids. [a]Treated with azithromycin in her skilled nursing facility at the beginning of the pandemic; [b]treated with remdesivir, convalescent plasma, admitted to intensive care and ventilated; [c]managed as high risk with decadron and bamlanivimab owing to recent rituximab infusion; [d]admitted to intensive care; [e]hospital course complicated by embolic stroke, deep vein thrombosis, pulmonary embolism; [f]recovered but BP flared, entered hospice care months later; [g]treated with tocilizumab and supplemental oxygen.

COVID-19 diagnosis. She was treated with azithromycin at the beginning of the pandemic in her skilled nursing facility before succumbing. A 65-year-old man with PV and obesity on mycophenolate mofetil who received rituximab 5 months prior was treated with decadron and bamlanivimab and recovered without hospitalization.

Altogether, six patients were treated with rituximab, three with mycophenolate mofetil, five with methotrexate (each alone or in combination with prednisone), and five with topical steroids alone or in combination with tetracycline antibiotics. All five patients treated with topical corticosteroid/tetracycline recovered. Two required hospitalization – a 99-year-old woman who had a BP flare after recovery and entered hospice care soon thereafter and a 102-year-old woman with BP treated with tocilizumab and supplemental oxygen. The five patients in the methotrexate group recovered at home. The three patients treated with mycophenolate mofetil recovered, one after intensive care unit admission, tocilizumab, high-dose steroids and ventilation, and one after a hospital course complicated by embolic stroke, deep vein thrombosis and pulmonary embolism.

The recovery of 17 of 19 patients with AIBD who had documented SARS-CoV-2 infection in our single institution cohort, despite advanced age and comorbidities, is reassuring. The two deaths were in individuals treated with rituximab < 6 months before infection, suggesting that recent rituximab therapy may increase risk of poor outcomes. These findings complement observations of decreased hospitalization rates of infected patients with AIBD with increasing intervals post rituximab[3] and a 4·04-fold increase in death among rheumatology patients on rituximab,[4] and likely reflect the kinetics of B cell reconstitution following depletion.[7] Thus, our data provide specific rational supporting expert guidelines to weigh the risks of rituximab relative to other immunosuppressive therapies for AIBD during this pandemic.[8]

Although larger datasets are needed, our observations suggest that patients on rituximab be counselled about the increased risks for poor COVID-19 outcomes. Patients should be vaccinated prior to therapy when possible, and dermatologists should consider confirming response with SARS-CoV-2 spike protein IgG serologies. Finally, the observations in this cohort, although small, provide rationale for the immediate use of COVID-19 monoclonal antibodies such as bamlanivimab, etesevimab, casirivimab and imdevimab after SARS-CoV-2 detection in dermatology patients treated with rituximab in the previous 6 months.

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Patient-reported skin reactions to 5% 5-fluorouracil in treatment of actinic keratosis

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Dear Editor, Skin reactions occur frequently during and after treatment of actinic keratosis (AK) with 5% 5-fluorouracil (5-FU). Managing expectations is important to prevent patients from prematurely terminating treatment and to ensure patients' adherence. The frequency and severity of skin reactions was evaluated using data from patients with AK who participated in a clinical trial comparing different field-directed therapies for AK and who were randomized to 5-FU cream.[1] A secondary objective was to evaluate whether more severe skin reactions were associated with a higher probability of treatment success.

5-FU was prescribed twice daily for 4 weeks and patients scored presence of skin reactions on a four-point scale or