for one individual who had to discontinue sirolimus treatment due to painful oral ulcers (grade 3).

Oral ulceration was experienced by the majority of patients in our study and has been frequently reported in prior prospective trials. mTOR inhibitor-associated stomatitis appears similar to aphthous ulceration and distinct from oral mucositis caused by chemotherapy. Acneiform eruptions have been reported in about one-quarter of patients taking mTOR inhibitors; our findings suggest that this may be more common than previously considered. Previous trials have also reported infections, particularly of the respiratory tract, and our results indicate that skin and soft tissue infections may occur. Remarkably, 20 (67%) experienced changes relating to the pilosebaceous unit, including changes in hair growth. This may result directly from mTOR inhibition through effects on hair follicle stem cells and hair follicle cycling, or indirectly through inhibition of signalling through epidermal growth factor (EGF). Several hair-related side-effects, including acne, trichomegaly and scalp hair changes, have been associated with EGF inhibitors. A potential limitation of our study is partial reliance on patient history for documenting side-effects. Furthermore, the retrospective nature of the study limited our ability to assess the timing and dose-dependence of side-effects.

Dermatological side-effects of oral mTOR inhibitors are common but generally do not necessitate treatment discontinuation. For side-effects that are particularly bothersome or complicated, routine monitoring by dermatologists can be vital for optimizing quality of life during therapy. Painful mouth ulcers that hinder oral intake may lead to poor nutrition. Patients may benefit from avoidance of foods that may traumatize the oral mucosa as well as from topical corticosteroids or analgesics. Acneiform eruptions, which may be painful and cause psychological distress, may be managed with conventional acne therapies. Patients should be cautioned prior to undergoing skin biopsies regarding the risks of poor wound healing and cutaneous infections. For individuals who are refractory to direct management of dermatological side-effects, dosage reduction or transient discontinuation of treatment may be pursued, especially if the risks of stopping therapy outweigh the benefits.

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Patients with bullous skin disease in a high-epidemic COVID-19 area, Bergamo, Italy

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Dear Editor, A severe outbreak of coronavirus disease 2019 (COVID-19) emerged in China in December 2019 and rapidly spread worldwide. The number of people with COVID-19 has dramatically increased in Italy, and it still remains a severe public health emergency.1,2 Bullous pemphigoid (BP) and
pemphigus vulgaris (PV) are blistering disorders associated with barrier disruption, immune dysregulation and use of immunosuppressing systemic therapy. Patients with BP and PV have higher potential risk factors for infections secondary to skin alterations, comorbidity, and chronic treatment with immunosuppressing agents.3

We decided to advise patients affected by bullous diseases to comply with hygiene rules and use of protective devices. We encouraged them to observe social distancing measures and discouraged spontaneous suspensions of ongoing therapy, and recommended they inform their dermatologist in case of onset of symptoms, as suggested by the Italian Society of Dermatologists4 and several papers.5–7 We report below our experience in Bergamo, a highly epidemic area for COVID-19.

Our patients with BP and PV are residents in the provinces of Bergamo (52 BP, 26 PV; 84%), Milan (6 BP, 0 PV; 6%), Brescia (2 BP, 2 PV; 4%), Lecco (1 BP, 1 PV; 2%), Cremona (1 BP, 1 PV; 2%) and Sondrio (0 BP, 1 PV; 1%) – areas of Lombardy with a high incidence of COVID-19.8 There were 62 patients with BP (34 male, 28 female; mean age 78.6 ± 10.1 years, range 52–98) and 31 with PV (17 male, 14 female, mean age 62.5 ± 16.4 years, range 19–95) (Table 1). All patients were contacted by telephone 45–50 days after the beginning of the spread of COVID-19 in the Bergamo area.

Ten patients with BP (16%) experienced suspected COVID-19 symptoms. Seven of these reported coming into contact with patients with suspected (n = 3) or known (n = 4, positive nasal swab) COVID-19. Six patients with BP (10%) experienced ‘mild-to-moderate’ symptoms (e.g. flu-like symptoms, cough, low-grade fever or anosmia/ageusia, resolved without hospitalization), and four patients with BP (6%) experienced ‘severe’ symptoms (e.g. pneumonia with respiratory failure) that needed hospitalization (all hospitalized patients received hydroxychloroquine). All hospitalized patients had a positive COVID-19 nasal swab; three of these patients died (5%, mean age 85–0 years). All of the patients who died had severe cognitive impairment; the mean age of patients with COVID-19 who died in our region was 79–0 years.8 In March 2020 in Italy, nasal swabs

Table 1 Characteristics of patients with bullous pemphigoid and pemphigus vulgaris

|                                      | Bullous pemphigoid (n = 62) | Pemphigus vulgaris (n = 31) |
|--------------------------------------|------------------------------|-----------------------------|
|                                      | Suspected COVID-19 symptoms  | Asymptomatic                | P-value  |
|                                      | (n = 10)                     | (n = 52)                    |          |
| Age (years), mean ± SD (range)       | 79.5 ± 11.2 (61–98)          | 78.0 ± 10.2 (52–95)         | 0.70     |
| Age at onset (years), mean ± SD (range) | 75.4 ± 10.1 (57–89)          | 75.7 ± 10.2 (51–94)         | 0.94     |
| Duration of disease (months), mean ± SD (range) | 48.4 ± 40.6 (13–113)        | 28.2 ± 26.5 (1–123)        | 0.04     |
| Male                                 | 60 (6/10)                    | 54 (28/52)                  | 0.72     |
| Contact with person with suspected or confirmed COVID-19 | 70 (7/10)                   | 2 (1/52)                   | < 0.001  |
| Principal comorbidities              |                              |                             |          |
| Diabetes                             | 30 (3/10)                    | 37 (19/52)                  |          |
| Hypertension                         | 30 (3/10)                    | 27 (14/52)                  |          |
| Neurological or psychiatric diseases | 30 (3/10)                    | 21 (11/52)                  |          |
| Cardiovascular diseases              | 30 (3/10)                    | 35 (18/52)                  |          |
| Chronic kidney failure               | 30 (3/10)                    | 6 (3/52)                    |          |
| Dyslipidemia                         | 20 (2/10)                    | 13 (7/52)                   |          |
| Neoplasia                            | 10 (1/10)                    | 6 (3/52)                    |          |
| Therapy                              |                              |                             |          |
| Systemic steroid                     | 60 (6/10)                    | 88 (46/52)                  | 0.03     |
| Dosage (mg per day), mean ± SDa      | 5.2 ± 1.7                    | 6.0 ± 3.6                   | 0.56     |
| Azathioprine                         | 0 (0/10)                     | 8 (4/52)                    | 0.36     |
| Doxycycline                          | 0 (0/10)                     | 12 (6/52)                   | 0.26     |
| Cyclophosphamide                     | –                            | –                           | 0 (0/7)  |
| Dapsone                              | –                            | –                           | 0 (0/7)  |

The data are presented as % (n/N) unless stated otherwise. Means and SDs were compared between patients using a t-test for independent samples. Categorical variables were summarized as the number and percentage of all patients and were evaluated using the χ²-test or Fisher’s exact test. Significance was set at P < 0.05. aPrednisone or equivalent.

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were taken only in hospitalized patients; serological tests are currently still limited to regional regulations.

Seven patients with PV (23%) experienced suspected symptoms of COVID-19. Four patients with PV (suspected or asymptomatic) reported contact with patients with suspected (n = 3) or known (n = 1) COVID-19. Six patients with PV (19%) experienced 'mild-to-moderate' symptoms (as described above) and one patient with PV (3%) experienced 'severe' symptoms that needed hospitalization. This patient (69 years old, comorbidity of previous breast cancer), confirmed with a positive COVID-19 nasal swab, has now recovered.

For all those taking systemic steroid therapy, the current dosage was not considered immunosuppressive (> 20 mg per day). No patient independently discontinued the current therapy for fear of recurrence of bullous lesions. Ongoing steroid or immunosuppressive therapy has been stopped for hospitalized patients. All patients with pemphigoid and pemphigus were in remission, even 10 newly diagnosed patients (duration of disease < 6 months). One patient with pemphigus had been treated with rituximab 6 months earlier; he reports no COVID-19 symptoms.

Observation of these data shows that the main risk factor for developing suspected COVID-19 symptoms was contact between the patient and an individual with known or suspected COVID-19. Furthermore, we have seen that longer disease duration is more frequently associated with patients with suspected COVID-19 symptoms. A longer duration of therapy, although not at immunosuppressive dosages, probably creates a condition of infectious risk predisposition. Contact with COVID-19 is probably the most important factor: in patients with BP we found statistical significance, while in patients with PV we found no significance but a consistent trend. It must be considered that, given that many tests were performed, it is possible that some lower P-values arose by chance. Observations of a larger number of patients will be required to evaluate whether these trends can be confirmed.

It is therefore important to create a communication channel with these patients to give clinical and human support and to help in managing therapies. We found it essential to advise and empower patients on activities that limit the risk of infection (hand hygiene, social distancing, use of protective devices), especially the most fragile, elderly and comorbid patients.

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Thrombotic occlusive vasculopathy in a skin biopsy from a livedoid lesion of a patient with COVID-19

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Dear Editor, Some authors have reported the presence of cutaneous lesions related to the new coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, in up to 20–4% of cases. However, these lesions are not well characterized either clinically or histopathologically. A recently highlighted finding is congested and oedematous blood vessels along with hyaline thrombi in the alveolar septum, and also in the heart, liver and kidney of three autopsied patients who died due to severe infection by SARS-CoV-2. Thus, anticoagulant treatment has been proposed to decrease mortality in certain cases of severe COVID-19 disease. We report a case of livedoid purple lesions along with acrocyanosis in a patient with confirmed SARS-CoV-2 infection with positive nasopharyngeal swab, showing an underlying obstructive cutaneous vasculopathy.