

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<sup>3</sup> and a 4.04-fold increase in death among rheumatology patients on rituximab,<sup>4</sup> and likely reflect the kinetics of B cell reconstitution following depletion.<sup>7</sup> 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.<sup>8</sup>

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.<sup>1</sup> A secondary objective was to evaluate whether more severe skin reactions were associated with a higher probability of treatment success.

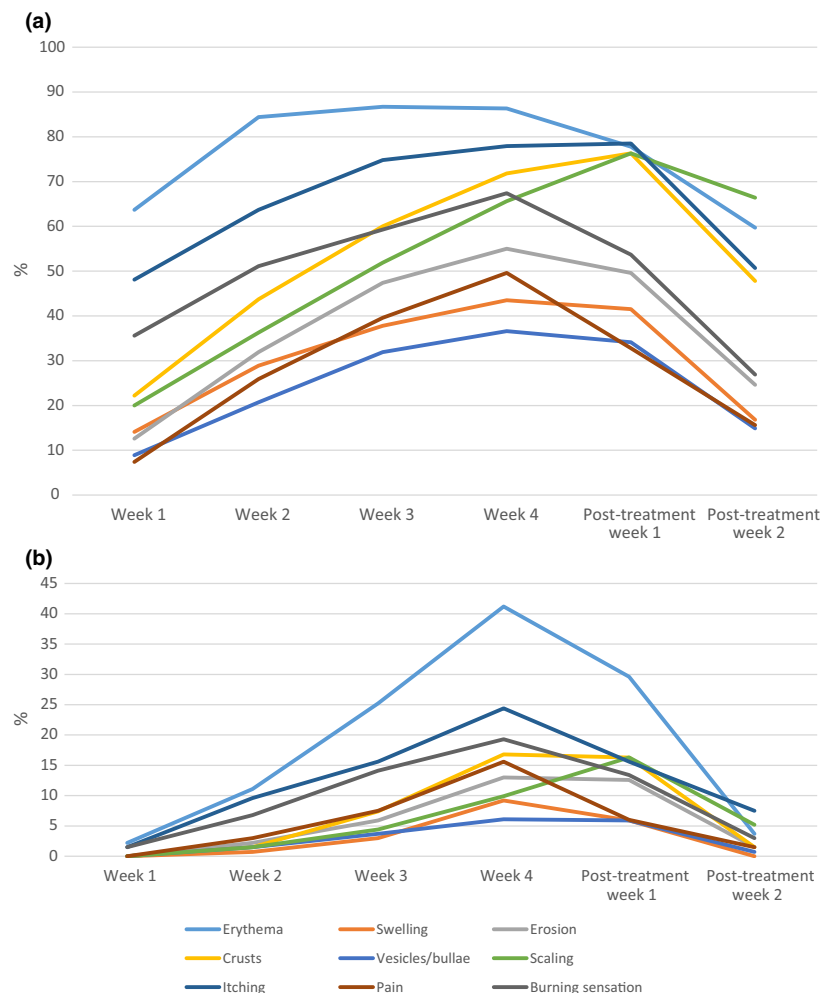
5-FU was prescribed twice daily for 4 weeks and patients scored presence of skin reactions on a four-point scale or

numeric rating scale (pain and burning sensation) during treatment and for 2 weeks post-treatment. Maximum scores were used for analysis, and categorized into absent (0), mild/moderate (0.1–6.0) and severe (6.1–10.0) skin reaction. Risk ratios with 95% confidence intervals (CI) and P-values were calculated to examine the association between the severity of skin reactions and probability of treatment success ( $\geq 75\%$  reduction in lesion numbers) 3 months post-treatment.

Of the 135 patients with complete diaries, 89.6% were male and the median age was 73 (range 48–90) years. Treatment success occurred in 111 patients for whom treatment response was known. Most patients (92.6%) reported full adherence to the treatment regimen. Severe erythema was reported most often, by 63 of 135 (46.7%) patients. Other commonly reported skin reactions were itching (28.9%), crusts (19.3%), burning sensation (21.5%) and scaling (18.5%) (Figure 1). The highest frequency and severity of skin reactions occurred in week 4 and the first week post-treatment (Figure 1).

Patients who reported severe or mild-to-moderate erythema had a higher probability of treatment success than patients without erythema. The relative chance of successful treatment was 1.90 (95% CI 1.02–3.55,  $P < 0.01$ ) and 1.54 (95% CI 0.82–2.91,  $P = 0.10$ ), respectively. After correction for potential confounding by age, number of AKs and adherence to the treatment regimen using multivariate logistic regression analysis, the adjusted odds ratios were very similar to the unadjusted odds ratios. Severe erythema occurred in 63.5% of patients with AK on the face vs. 36.5% of patients with AK on the vertex, but adjustment for location was not possible because none of the patients with AK on the face had a treatment failure.

Our results show that many patients experience skin reactions during and after 5-FU treatment. All skin reactions showed a peak after 4 weeks. For most patients, skin reactions in the first 2 weeks were still acceptable regarding the impact on facial appearance as well as discomfort. This information may be useful to discuss with patients before treatment, as it may help them in scheduling the treatment period.




**Figure 1** Patient-reported weekly presence of (a) any skin reaction, and (b) severe skin reactions during and post-treatment in percentages. Skin reactions were scored on a four-point scale (absent, mild, moderate or severe) or numeric rating scale (0–10; pain and burning sensation) and categorized into absent (0), mild/moderate (0.1–6.0) or severe (6.1–10.0).

As mentioned in previous studies, (fear of) side-effects can be a reason for nonadherence to patient-applied topical treatments.<sup>2,3</sup> Although generally side-effects cannot be avoided in order to achieve effective treatment, knowledge about the course of side-effects can help to inform and educate patients, and ultimately increase adherence and thus the probability of a favourable treatment outcome.

Among the skin reactions to 5-FU cream severe erythema stands out as the reaction that is most strongly and significantly associated with an increased probability of treatment success. Similar results were seen in patients treated with imiquimod cream in the trial (data not shown). This finding can be used to reassure patients who experience severe reactions, especially erythema. Erythema is an important indicator of inflammation and the hypothesis that inflammation is required to achieve a therapeutic effect has been corroborated by findings in previous publications.<sup>4,5</sup>

In current guidelines, daily application of 5-FU is recommended for 3 to 4 weeks.<sup>6–8</sup> In daily practice the treatment duration is often shorter as it depends on the severity of the skin reactions. However, it is unclear whether patients who end treatment prematurely owing to severe skin reactions achieve efficacy.<sup>8</sup> The initial treatment success rate after 5-FU treatment twice daily for 4 weeks in this study population was 85.2%, and relatively high compared with other studies.<sup>1</sup> We would therefore not recommend a shorter treatment period in patients with severe skin reactions, unless new evidence suggests that a shorter treatment regimen suffices in these patients.

In conclusion, we highlight the importance of patient education on the frequency, severity and timing of skin reactions during and after treatment of AK with 5-FU cream in order to increase patient adherence to the prescribed regimen and thus treatment effectiveness. Moreover, we found that more severe erythema as a skin reaction is associated with a higher probability of treatment success.

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## Characteristics of patients with psoriasis with Psoriasis Area and Severity Index < 10 treated with biological agents: results from the French PsoBioTeq cohort

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DEAR EDITOR, The decision to initiate systemic therapy in psoriasis is based mainly on disease severity assessments, determined using physician-derived scores. A commonly used assessment is the Psoriasis Area and Severity Index (PASI), with an absolute value of 10 or more indicating severe disease.<sup>1</sup> How patients perceive the severity of psoriasis and physicians' evaluations may be discordant, especially when lesions involve visible areas or are associated with itching. Such lesions can have a greater impact on quality of life (QoL),<sup>2</sup> as evaluated using patient-reported outcomes such as the Dermatology Life Quality Index (DLQI). Analysis of the Swedish PsoReg registry found that patients with high PASI and low DLQI were more likely to receive biologics than those with low PASI and high DLQI.<sup>3</sup> A retrospective study of 54 patients showed that DLQI guides therapeutic decisions in patients with PASI ≤ 6, with improvement of both disease and QoL scores following systemic therapy.<sup>4</sup> A recent international Delphi consensus challenged the severity criteria,<sup>5</sup> and guidelines<sup>1,6</sup> propose considering systemic therapy when psoriasis involves impactful areas or is recalcitrant to topical therapy, whatever the PASI.

To understand better the determinants of clinical decisions other than disease severity, we aimed to describe the clinical