(levocetirizine 15 mg per day), and reported an acceptable positive response of both skin diseases at the 6-month follow-up: clinical examination showed that the AU and AAK were well and partly controlled, respectively.

AU is a rare type of chronic inducible urticaria. Currently, the pathomechanism remains unclear, although there is some evidence that water acts as a carrier for an epidermal antigen that causes histamine release. Recent studies also mention a histamine-independent mechanism based on the cholinergic pathway. Acetylcholine plays a role in initiating sweating and may produce degranulation of mast cells around sweat glands, thus releasing histamine and producing hives.

AAK is a rare aquagenic cutaneous disorder, mainly located on the palms and/or soles, in which hyperhidrosis is often found. The pathogenesis of AAK is also unknown, but it is thought that an aberrant function of the sweat glands may be involved. Histological examination shows orthokeratotic hyperkeratosis, dilated eccrine ducts, hyperplasia of eccrine coils and crenulated appearance of their luminal cells. Translocation of the protein aquaporin 5 (AQP5) is essential in sweat secretion from eccrine glands. Kabashima et al. reported that AQP5 is present exclusively in the dark cells of sweat glands of healthy patients, and with regard to AAK, they found an aberrant expression of AQP5 that also extends to the clear cells of sweat glands. An association between AU and AAK has not been reported in recent scientific papers.

We suggest that there may be a common unknown pathogenic mechanism between AAK and AU with a cholinergic basis. This hypothesis is still highly speculative. Acetylcholine may be involved in AU but the exact mechanism still not fully understood. Aberrant expression of AQP5 may lead to dysregulation of the sweating mechanisms in AAK. Additionally, phosphorylation of AQP5 depends on the activation of M3-muscarinic receptors in the eccrine sweat gland by acetylcholine.

In conclusion, we report a case of concurrent AU and AAK, which has not been reported previously, to our knowledge.

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The ‘number needed to treat’ metric: a further marker of the impact of COVID-19 on malignant melanomas
doi: 10.1111/ced.15186

Linked article: Bowe S et al. Clin Exp Dermatol 2022; doi: 10.1111/ced.15146

Dear Editor,

We read with interest the recent article published in Clinical and Experimental Dermatology by Bowe et al., describing the impact of the COVID-19 pandemic on malignant melanoma (MM) services in Ireland. We wish to add our experience of the impact of the COVID-19 pandemic on MM services, and to highlight the value of the ‘number needed to treat’ (NNT) as a metric to further analyse this.

All patients with suspicious pigmented lesions (PL) who were referred electronically [using the National Cancer Control Programme (NCCP) referral form] to dermatology rapid access skin cancer clinics, were identified during 6-month timeframes (March–August) in both 2018 and 2020.

Bowe et al. reported a 27% decline in PL referrals between 2019 and 2020, with continued decline through 2021. Although we observed a 58% decline in PL referrals during the initial containment and lockdown phase of the COVID-19 pandemic in April 2020 compared with similar timeframe in April 2018, we found that, as government restrictions eased, there was a five-fold increase in PL referrals from April (n = 17) to August (n = 89) 2020 (Fig. 1). The total number of referrals received electronically in our institution in 2020 (n = 864) was 27% higher than in 2018 (n = 632). This upward trend in referrals has continued, with total electronic PL referrals received in 2021 (n = 1280) being more than double the
total received in 2018 \( (n = 632) \) and a third higher than referrals received in 2020.\(^1\)

Like Bowe et al., we observed the negative impact of the COVID-19 pandemic on MM stage at time of diagnosis. We previously reported a 41% reduction in the total number of Stage 1 MMs (according to the Cancer Staging Manual, eighth edition\(^4\)) diagnosed in 2020 \( (n = 74) \) compared with 2019 \( (n = 44) \).\(^2\) Although the total numbers of MMs were small, there was a trend towards higher Breslow thickness (BT) at time of diagnosis, with a monthly mean BT of 2.1 mm in 2018, increasing to 3.1 mm in 2020.

In 2018, 23 invasive MMs and 240 benign lesions were diagnosed during the 6-month study period, producing an NNT ratio of 9.6. In 2020, melanoma diagnoses remained stable, but there was a 56% drop in benign lesions, producing an NNT of 4.5 in 2020 (Table 1). The halving of the NNT highlights a pandemic-induced streamlining of dermatology services to focus on delivery of urgent skin cancer care. A low NNT raises concerns regarding potentially missed cases, and may reflect patients’ reluctance to attend healthcare services during a period of societal restrictions and concerns regarding infection risk.

We agree with our colleagues, Bowe et al., that continuous evaluation of the impact that the pandemic has had on MM services is critical. We report the value of the NNT metric as an underused tool to assess resource efficiency, diagnostic accuracy and practice standards, which is of particular significance when faced with the challenges of the COVID-19 pandemic. We are concerned by the trends towards later-stage MM at the time of diagnosis, but our experience of continued increased in our PL referrals would suggest that patients in our catchment area are no longer reluctant to access healthcare services as the pandemic seems to be moving to an endemic status.

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### Conflict of interest

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none.

### Table 1

| Month   | 2018 | 2020 |
|---------|------|------|
|         | Benign | MM | Total | NNT | Benign | MM | Total | NNT |
| March   | 28 | 6 | 34 | 9.6 | 20 | 5 | 25 | 4.5 |
| April   | 24 | 4 | 28 | 6 | 1 | 7 |
| May     | 39 | 5 | 44 | 9 | 6 | 15 |
| June    | 30 | 2 | 32 | 27 | 4 | 31 |
| July    | 52 | 1 | 53 | 13 | 3 | 16 |
| August  | 47 | 5 | 52 | 21 | 2 | 23 |
| Total   | 220 | 23 | 243 | 96 | 21 | 117 |

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An 80-year-old man presented with lesions on his scalp. Over the next year, new primary SCCs had undergone evaluation of several skin lesions on his scalp, for which shave biopsies had demonstrated well-differentiated SCCs as well as dermal in-transit metastases. He had opted for chemotherapy and radiation to his scalp. Over the next year, new primary SCCs had excised from the dorsa of both hands, and positron emission tomography had revealed additional metastatic lesions in paratracheal lymph nodes and vertebrae. Six weeks before his presentation, he has been started on intravenous cemiplimab 350 mg every 3 weeks, with radiological response demonstrated within 1 month. The patient also had diabetes treated with insulin, and hypertension treated with amldipine and carvedilol.

On physical examination, pruritic red papules, vesicles, bullae and erosions were seen, clustered at previous sites of keratinocyte carcinoma on the right deltoid (Fig. 1a) and right hand (Fig. 1b) as well as scattered lesions on the scalp. Other sites of previous trauma were spared. Histopathological examination of punch biopsies of vesicles on the hand and scalp demonstrated subepidermal bullae and numerous eosinophils. Direct immunofluorescence from perilesional skin showed linear IgG and C3 along the epidermal basement membrane confirming the diagnosis of drug-induced bullous pemphigoid.

The patient was treated with doxycycline 100 mg plus niacinamide 500 mg twice daily along with topical corticosteroids. After a brief pause of cemiplimab therapy due to gastrointestinal adverse effects, immunotherapy was resumed.

Development of immune-related adverse events is common with checkpoint inhibitors. Multiple dermatological eruptions have been reported, including bullous pemphigoid (BP). About 1% of patients treated with programmed cell death protein (PD)-1 inhibitors develop bullous disorders. In this case, the tropism for sites of previous keratinocytes appears to be novel.

Immune-related BP following anti-PD-1 therapy could be related to a common target antigen located at the dermoepidermal junction in addition to tumour cells. This patient demonstrated bullae in the footprint of treated keratinocyte carcinomas, a phenomenon that has not been previously identified. Localized BP was reported at a site of prior radiation treatment for melanoma metastases in a patient who had received pembrolizumab followed by nivolumab. Apoptosis of epidermal cells following radiation may preferentially expose BP180 antigens to immune surveillance via radiation-resistant Langerhans cells.

It is possible that our patient’s eruption began as localized immune dysregulation secondary to disruption of rapidly dividing tumour cells. Tissue-resident memory T cells may have been recruited by the tumours and played a role in initiating a localized pemphigoid after evasion of regulatory T-cell surveillance permitted by PD-1 blockade. These foci of local dysregulation of immune control of damaged skin would be an example of and ‘immuno-compromised district’ described by Ruocco et al. We believe this response would be best termed an ‘iso-oncotopic response’ and was likely to be the result of a complex interplay of residual immune factors recruited by tumours but still present in newly formed scars around partially or completely treated skin cancers.