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Immunomodulatory and/or immunosuppressive drugs should not be stopped prior to skin tests for the assessment of drug allergy

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DEAR EDITOR, The use of immunomodulatory and/or immunosuppressive therapy (IT) is increasingly common in the management of chronic inflammatory disease. Skin reactions to any drug (IT or not) are not rare in these patients, justifying allergological investigations. The influence of IT on allergological tests for drugs is not clearly described and IT cannot be interrupted due to the underlying disease. The data assessing the benefit and the safety of allergological testing for drug allergy in patients under IT are missing.

We conducted a bicentric retrospective observational study in the Dermatology departments of Lille University Hospital and Rouen University Hospital between 2011 and 2019. We included all patients who underwent allergological tests including skin tests (ST): patch tests (PT), skin prick tests (SPT), intra-dermal test (IDT); and/or oral provocation test (OPT), and who were under treatment with IT. In Lille, patients were included from the clinico-pharmacological database. In Rouen, patients were included from the Clinical Dataware House (EDSaN) with a cross-search using the keywords in narrative documents: 'allergic tests' and 'immunosuppressive therapy' (list of drug commercial names or substances).¹ ST were performed in the same way in the two centres according to the international guidelines.^{2,3} All included patients ($n = 61$) gave written

consent for allergological investigations and were informed of the potential use of the data for research purposes. The study was approved by the French 'commission nationale de l'informatique et des libertés' under the reference DEC21-175.

Detailed information is shown in Table 1 and its notes. The median time between eruption and ST was 300 (153–710) days. The median time between the beginning of IT and ST was 507 (233–1626.0) days. The main systemic IT not interrupted during allergological tests were corticosteroids (prednisolone and prednisone). The main conditions requiring the continuation of IT were organ transplant. The most frequently tested drugs were antimicrobials. PT were performed in 18 patients (29.5%), SPT in 52 patients (85%), IDT in 57 patients (93%) and OPT in 38 patients (62%). Thirteen (21%) patients had at least one positive ST, including three (17%) PT, one (2%) SPT, 10 (17.5%) IDT and two (5%) OPT. Of these 13 patients, the reaction was immediate in four (31%) and delayed in 11 (85%); two had both immediate and delayed reactions to the same drugs. The calculated negative predictive value for ST was 94.7%, 95% confidence interval 87.5–100, $P < 0.05$.

The main continued IT in patients with positive ST were prednisolone or prednisone (eight of 13: 5–20 mg daily), azathioprine (100–150 mg daily), ustekinumab, methotrexate (15 mg/week), adalimumab, mycophenolate mofetil (from 750 mg to 1 g daily), belimumab, tacrolimus, hydroxychloroquine. IT were combined for six patients. Among the 38 patients contactable by telephone, most (22, 58%) reported a safe real-life reintroduction of the negative tested drug compared with 16 patients who had not restarted the treatment yet (fear, or not indicated treatment). The reintroduced drugs were penicillin (nine), iodinated contrast media (six), proton pump inhibitors (two), immunosuppressant agents [one each: methotrexate, tocilizumab, tumour necrosis factor (TNF) inhibitors] and paracetamol (two). A mild erythema with pruritis was reported by one patient during the real-life OPT for amoxicillin/clavulanic acid while PT, SPT and IDT were negative.

These results highlight the interest of performing ST in this population, while the interruption of IT is usually recommended before testing. The main strength of our study is the homogeneous way to perform ST in both centres. Few publications assessed the effect of IT on ST and the data concerned exclusively PT performed for allergic contact dermatitis.^{4,5} As in our study, these studies suggested that ST could be positive even in patients treated with IT. Concerning contact dermatitis, the experts from the North American Contact Dermatitis Group recommend avoiding corticosteroids for 3–5 days if possible or performing PT on maximum oral prednisone dosage of 10–20 mg daily but evidence is lacking. They considered a dose effect on PT for azathioprine, ciclosporin, mycophenolate mofetil and tacrolimus and little or no effect for methotrexate, anti-TNF- α and ustekinumab. However, all these recommendations and data could not be extrapolated to all procedures of ST (SPT, IDT, OPT) and to the context of drug-induced reactions in which various pathophysiological mechanisms are involved.⁶ We assume that the heterogeneity of our real-life population (type of IT and culprit drugs,

Table 1 Patient characteristics, type of hypersensitivity reaction, underlying diseases

Parameter	Values, N = 61, n (%)
Sex	
Male	18 (30)
Female	43 (70)
Mean age	52 years
University hospital centre	
Lille	42 (69)
Rouen	19 (31)
Type of hypersensitivity reaction	
Immediate hypersensitivity	28 (45.9)
Urticaria	9
Angio-oedema	8
Urticaria and angio-oedema	7
Anaphylactic shock	2
Facial erythema	1
Pruritus	1
Delayed hypersensitivity	28 (45.9)
Maculopapular exanthema	22
DRESS syndrome	3
Purpura	1
AGEP	1
Erythroderma	1
Overlap immediate and delayed hypersensitivity	1
Unknown reaction	4
Underlying diseases ^a	
Organ transplant	15 (25)
Crohn disease	8 (13)
Systemic lupus erythematosus	6 (10)
Psoriasis	6 (10)
Rheumatoid arthritis	5 (8)
Autoimmune hepatitis	3 (5)
Multiple sclerosis	3 (5)
Hidradenitis suppurativa	2 (3)
Other ^c	13 (21)
Tested drugs	
Antimicrobials ^d	37 (61)
Iodinated contrast media	12 (20)
Immunomodulatory molecules ^e	14 (23)
Proton pump inhibitors	2 (3)
Nonsteroidal anti-inflammatory drugs	2 (3)
Gadolinium contrast agents	2 (3)
Others ^f	9 (15)

AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; IT, immunomodulatory and/or immunosuppressive therapy; TNF, tumour necrosis factor ^aIT not interrupted during allergological tests [(n, %) of N = 61]: corticosteroids (prednisolone and prednisone) at mean dosage of 10.5 mg per day (31, 51%), mycophenolate mofetil (16, 26%), biological therapies (19, 31%) [including TNF- α inhibitors like infliximab^b (4), adalimumab (4), certolizumab^b (2); ustekinumab (3), belimumab (4), belatacept (1) and obinituzumab^b (1)], tacrolimus (13, 21%), methotrexate (7, 11.5%), hydroxychloroquine (4, 6.5%), azathioprine (3, 5%), fingolimod^b (2, 3%), lenalidomide (2, 3%), ciclosporin (2, 3%), leflunomide^b (1, 1.5%), everolimus (1, 1.5%), thalidomide^b (1, 1.5%) and mesalazine^b (1, 1.5%). ^bNegative allergological tests under these IT. ^cUnderlying diseases (one instance of each): Horton's disease, anti-phospholipid syndrome, bone metastases, brain metastases, systemic scleroderma, juvenile arthritis, rhizomelic arthritis, nephrotic syndrome, periarteritis nodosa, immunological thrombocytopenic purpura, follicular lymphoma, allogeneic stem cell transplant, multiple myeloma. ^d β -lactams, macrolides, glycopeptide, oxazolidinones, cyclic lipopeptide, lincosamides, streptogramin, imidazoles, aminoglycosides and rifamycin. ^eThalidomide, rituximab, methotrexate, corticosteroids, tocilizumab, etanercept, certolizumab, golimumab, hydroxychloroquine. ^fAntiemetics, antihistamines, analgesics, anti-arrhythmic, antiepileptics and antihypertensive drugs.

underlying disease, clinical features of drug-induced reaction and the global sensitivity of ST) did not allow us to form a strong conclusion about each IT drug. In our experience, ST performed under IT were safe and led to well-tolerated reintroduction of drugs. This study emphasizes the service rendered by ST when IT could not be interrupted.

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Accuracy of commercially available smartphone applications for the detection of melanoma

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DEAR EDITOR, Artificial intelligence (AI) has shown promise in the analysis of images for detection of melanoma.¹ The

number of available dermatology smartphone applications ('apps') is rapidly growing and there is increasing interest in apps that provide diagnosis or triage of skin lesions.^{2,3} A 2020 systematic review found that nine studies evaluating six apps had poor study design and high risk of bias.³ To date, no studies have evaluated the accuracy of apps using an independent test set of clinical images comparable with those submitted through smartphones.

Based on a futility analysis (H1: mean sensitivity and specificity ≥ 0.5) with a conditional power threshold of 20%, we included clinical images of 15 consecutive histologically proven invasive melanoma cases (pT1a–pT2b) and 15 histologically proven benign naevi, all in patients with lighter skin phototypes. We identified five images of benign naevi in patients with skin of colour (SoC), diagnosed clinically by two dermatologists. Images were obtained as part of usual care at Memorial Sloan Kettering Cancer Center and retrieved from our image database. Median age was 56 years (range 23–87), and 21 patients (60%) were female. Images were cropped to the lesion and are available at the International Skin Imaging Collaboration Archive (<https://doi.org/10.34970/401946>). Local institutional review board approval was obtained.

Publicly available smartphone and web-based dermatology apps offering AI diagnostics were identified by querying the Apple App store, Google Play store and Google Search. Images were downloaded to an Apple iPhone 11, a Samsung Galaxy S10 and a Microsoft Windows 10 PC, and uploaded to each app. Metadata regarding lesion location, morphology and history were entered when required. If apps did not allow image upload from camera roll, images were displayed on a 4K ultra-high-definition monitor and captured via smartphone.

For apps that output one or more diagnoses, accuracy was calculated based on the presence or absence of melanoma in the top-1 or top-3 diagnosis. For apps that provided risk-category outputs, all possible category combinations were binarized as a positive or negative melanoma output. For apps that returned a continuous risk score, accuracy was calculated based on a cutoff of $\geq 50\%$ constituting melanoma.⁴ Indeterminate outputs were classified as benign. Apps that provided multiple output types were evaluated separately for each.

Of 43 apps identified, 25 claimed to identify melanoma and were functional. Of these, 10 did not allow upload from camera roll and eight required metadata. Four apps rejected ≥ 1 image. Fifteen of 25 apps returned diagnoses, 12 of 25 risk categories and two of 25 risk scores (Figure 1). Three apps gave >1 output type.

Across top-1 measures for all apps, mean sensitivity was 0.28 [95% confidence interval (CI) 0.17–0.39], mean specificity was 0.81 (95% CI 0.71–0.91) and mean accuracy was 0.59 (95% CI 0.55–0.62) (Figure 1). For diagnosis-based apps, risk-category-based apps and score-based apps, mean accuracy was 0.56, 0.60 and 0.64, respectively. In the 10 apps that returned at least three ranked diagnoses, mean top-1 accuracy (0.56) was higher than mean top-3