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References

- 1 Tregoning JS, Brown ES, Cheeseman HM *et al.* Vaccines for COVID-19. *Clin Exp Immunol* 2020; **202**: 162–192.
- 2 Polack FP, Thomas SJ, Kitchin N *et al.* Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383**: 2603–2615.
- 3 Widge AT, Roupael NG, Jackson LA *et al.* Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2021; **384**: 80–82.
- 4 EADV Task Forces statements on COVID-19 Vaccination. URL <https://eadv.org/cms-admin/showfile/COVID-19%20VACCINATION-TF%20ADVICE.pdf> (last accessed: 5 February 2021).
- 5 Furer V, Zisman D, Kaufman I *et al.* Immunogenicity and safety of vaccination against seasonal influenza vaccine in patients with psoriatic arthritis treated with secukinumab. *Vaccine* 2020; **38**: 847–851.
- 6 Gomez EV, Bishop JL, Jackson K *et al.* Response to tetanus and pneumococcal vaccination following administration of ixekizumab in healthy participants. *BioDrugs* 2017; **31**: 545–554.
- 7 Subesinghe S, Bechman K, Rutherford AI, Goldblatt D, Galloway JB. A Systematic review and meta-analysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. *J Rheumatol* 2018; **45**: 733–744.
- 8 Anderson EJ, Roupael NG, Widge AT *et al.* Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* 2020; **383**: 2427–2438.
- 9 Chernyshov PV, Tomas-Aragones L, Augustin M *et al.* Position statement of the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes on quality of life issues in dermatologic patients during the COVID-19 pandemic. *J Eur Acad Dermatol Venereol* 2020; **34**: 1666–1671.
- 10 Chiricozzi A, Gisondi P, Bellinani F, Girolomoni G. Immune response to vaccination in patients with psoriasis treated with systemic therapies. *Vaccines (Basel)* 2020; **8**: 769.

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Risk of severe allergic reactions to COVID-19 vaccines among patients with allergic skin diseases – practical recommendations. A position statement of ETFAD with external experts

Dear Editor,

Since the introduction of active vaccination against SARS-CoV-2 infection, there has been a debate about the risk of developing severe allergic or anaphylactic reactions among individuals with a history of allergy.^{1,2} Indeed, rare cases of severe allergic reactions have been reported in the United Kingdom and North America.³ By February 2021, a rate of 4.5 severe allergic reactions

occurred among 1 million patients vaccinated with the mRNA-based COVID-19 vaccines,^{1,3} which is higher than the generally expected rate of severe allergic reactions to vaccinations of around one in 1 million.^{4,5}

Warnings have subsequently been issued that ‘persons with severe allergies’ should not be vaccinated, leading to confusion among patients and vaccinating physicians.

Therefore, the European Task Force Atopic Dermatitis (ETFAD) – in addition to a statement on the use of systemic immunomodulatory treatments for atopic dermatitis (AD) during COVID-19 vaccination⁶ – discusses the putative risk of severe allergic reactions to COVID-19 vaccines for patients suffering from allergic skin diseases and give practical recommendations.

Generally, systemic allergic reactions to vaccines are rare, and due to hypersensitivity to components of the formulation of the vaccine such as conjugating agents, preservatives, metals, stabilizers, adjuvants and contaminants.⁵ In the case of COVID-19 vaccines, apart from the mRNA, the protein or the vector, one possible elicitor of anaphylaxis could be other ingredients as, for example, polyethylene glycol (PEG) present both in the BioNTech/Pfizer (Comirnaty) and the Moderna (mRNA-1273) vaccines; other additives may be contained in vaccines under development like AZD-1222, NVX-CoV2373 or Ad26.DOV2.S. Based on the available data, the safety and tolerability of COVID-19 vaccines appear to be better than that of, for example, smallpox vaccines.^{7,8}

The general recommendation is that AD patients should be vaccinated according to their local or national vaccination plan.^{6,7} Patients suffering from allergic skin diseases including AD do not per se have an increased risk of anaphylactic reactions to any COVID-19 vaccine. Precautions should be taken where patients have a history of anaphylaxis to drugs in general, especially to vaccinations, and in patients with systemic mastocytosis or idiopathic anaphylaxis. All these patients should undergo a drug allergy diagnostic work-up for allergy prior to vaccination.^{2,5}

Patients with an acute flare of eczema should be actively treated for their AD but vaccination should not be delayed in these patients. The same holds true for patients with urticaria and other allergic diseases.⁵

In selected cases, the use of anti-allergic medication prior to vaccination, such as combined histamine H1 and H2 receptor antagonists plus oral glucocorticoids – may be considered, as it is done in peri-operative anaphylaxis or severe reactions to radiographic contrast media.⁹ Such patients should be observed for 30 min after the vaccine injection.

Clear contraindications exist at the moment only for patients with documented severe allergic reactions to ingredients of the respective COVID-19 vaccine.

In the case of anaphylaxis, acute treatment includes intramuscular epinephrine as main pharmacotherapy. Epinephrine auto-injectors should be available at the vaccination centres as well as

other anti-allergic drugs and balanced electrolyte solutions for volume replacement.^{9,10}

Nearly all patients with allergic skin diseases can be vaccinated with the registered COVID-19 vaccines available today. Precautionary measures should be taken in a very small subgroup of patients, especially in those with possible severe allergy to ingredients of the vaccine. Knowledge about anaphylactic side-reactions should be improved among physicians and medical health personnel in COVID-19 vaccination centres.

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Conflict of interests

Dr. Ring has been an advisor or speaker for AbbVie, Allergika, Sanofi-Genzyme, Pfizer, Bencard, LEO Pharma, and Mylan. Dr. Thyssen has attended advisory boards for Eli-Lilly, Regeneron, Pfizer, LEO Pharma, Abbvie and Sanofi-Genzyme, received speaker honorarium from LEO Pharma, Abbvie, Regeneron, and Sanofi-Genzyme, and received research grants from Regeneron and Sanofi-Genzyme. Dr. Vestergaard has been investigator, speaker, or consultant for Novartis, Abbvie, Sanofi, LeoPharma and Eli Lilly. Dr. Barbarot has been a principal investigator, advisory board member, or consultant for Pierre Fabre Laboratory, Bioderma, Laboratoire La Roche Posay, Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo-Pharma, Pfizer, Amgen, Lilly. Dr. de Bruin-Weller has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzym. Dr. Bieber has been a principal investigator, advisory board member, or consultant for Regeneron, Sanofi, GSK, Celgene, Abbvie, AnaptysBio, MedImmune, Chugai, Pierre Fabre, Novartis, Asana Biosciences, LEO, Galapagos/MorphoSys, BioVerSys, Galderma, Kymab, Glenmark, Astellas, Daiichi-Sankyo, Lilly, Pfizer, MenloTx, Dermavant, Allmiral. Dr. T. Bieber was speaker, and/or consultant and/or Investigator for AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Böhringer-Ingelheim, Celgene, Daichi-Sankyo, Dermavant/Roivant, DermTreat, DS Pharma, RAPT/FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Kymab, LEO, Lilly, L'Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, Sanofi/Regeneron, UCB. T. Bieber is founder of the non-profit biotech company "Davos Biosciences". Dr. Gutermuth has been a consultant, advisory board member and/or speaker for AbbVie, Almirall, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme. Dr. Täieb has been a consultant or investigator for Pierre Fabre, Galderma, Novartis, Johnson and Johnson, Incyte, Abbvie, Modilac, Pfizer, Lilly, Arena, Bioderma, Sanofi. Dr. Seneschal has been an investigator, speaker, or consultant for Novartis, Abbvie, Sanofi, LeoPharma and Eli Lilly. Dr. Weidinger has received institutional research grants from LEO Pharma and L'Oréal, has performed consultancies for Sanofi-

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References

- 1 Anonymous. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, december 14–23, 2020. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 46–51.
- 2 Worm M, Ring J, Klimek L *et al*. Covid-19 vaccination and risk of anaphylaxis - recommendations for practical management. *MMW Fortschr Med* 2021; **163**: 48–51.

- 3 Silberman E. Serious COVID-19 Vaccine Reactions are Rare, Says New CDC Report. *ABD News via Yahoo News*; 2021.
- 4 Dreskin SC, Halsey NA, Kelso JM *et al.* International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J* 2016; **9**: 32.
- 5 Klimek L, Akdis C *et al.* ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines – an EAACI-ARIA position paper. *Allergy* 2021; 1–5. <https://doi.org/10.1111/all.14726>
- 6 Thyssen J, Vestergaard C, Barbarot S *et al.* European Task Force on Atopic Dermatitis (ETFAD): position on vaccination of adult patients with atopic dermatitis against COVID-19 (SARS-CoV-2). *J Eur Acad Dermatol Venereol* 2021; **35**: in press.
- 7 Wollenberg A, Christen-Zäch S, Taieb A *et al.* ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol* 2020; **34**: 2717–2744.
- 8 Polack FP, Thomas SJ, Kitchin N *et al.* Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *New Engl J Med* 2020; **383**: 2603–2615.
- 9 Ring J, Beyer K, Biedermann T *et al.* Guideline (S2k) to acute management and prevention of anaphylaxis - Update 2021. *Allergo J Int* 2021; **30**: 1–25.
- 10 Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2021; **384**: 643–649.

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LETTERS TO THE EDITOR

May melanophages hinder the subclinical spread of lentigo maligna and lentigo maligna melanoma? Results from a pilot study

Dear Editor

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) are renowned to present a subclinical spread that often extends widely in the surrounding photodamaged skin.

Previous studies showed that subclinical spread of melanoma was associated with lesion size,^{1–3} ill-defined margins,⁴ head and neck or central face localization,^{3,5,6} patient age ≥ 60 –65 years,^{2,6} phototype III–IV,⁵ incompletely excised or recurrent tumours,^{1,4} history of previous treatment,⁶ nests formation,⁴ dermal invasion¹ and ≥ 1 mitoses/mm².⁶ To analyse more thoroughly this argument, we performed a prospective study evaluating clinical, dermoscopic and histological features associated with subclinical spread of LM and LMM of the face.

The study was conducted at the Instituto Valenciano de Oncología from the 1st of January 2019 to the 1st of September 2019. In this period, we collected all LMs and LMMs of the face treated with staged micrographic/margin-controlled excision (SMEX).^{7,8}

Subclinical spread of melanoma was measured relying on the number of surgical stages required to obtain clear margins. This number defined our study groups. The variables that were

analysed and their association with number of surgical stages are described in Table 1. Spearman's Rho test was used to evaluate correlations between all variables. Differences in the distribution of each variable between the study groups were assessed by Mann–Whitney *U*-test, if quantitative, and by contingency tables, if categorical. Significance of contingency tables was analysed by chi-squared and Fisher's exact tests. All tests were two-sided, and the level of significance was set at $\alpha < 0.05$. Statistical analyses were performed using IBM SPSS 20.0.

During the 8-month period of study, we enrolled 12 patients, 5 males and 7 females, with an average age of 73 years. Three out of twelve presented dermal invasion and thus were diagnosed as LMM.

Four patients required 2 stages of SMEX to obtain surgical margins free of neoplasia. None required more than 2 stages.

Statistical analysis did not reveal any significant correlation of clinical and dermoscopic features with number of SMEX stages. Nevertheless, all the 4 lesions in our series that required two surgical stages presented ill-defined clinical margins. This was indeed associated with higher number of surgical stages.⁴

Among histological variables, we found a statistically significant inverse association between the presence of melanophages and the number of SMEX stages. None of the 4 patients that needed two surgical stages showed one or more melanophages in their pathological sections, while just 1 out of 8 of those that required one stage did not present these cells.

This finding could be explained because melanophages increase pigmentation of lesions, making them better clinically and dermoscopically defined. However, in our series, we found no significant association between the presence of melanophages and predominantly dark or ill-defined lesions (data not shown).

On the other hand, melanophages may directly hinder the subclinical spread of neoplastic cells. As melanin-laden macrophages, they reflect an immune response against neoplastic melanocytes (Fig. 1). How macrophages interact with melanomas is still a matter of debate, mostly because of their different biological behaviour depending on their polarization (M1 or M2 subtype). Remarkably, M1 macrophages seemed to possess pro-inflammatory and tumoricidal properties.⁹ Thus, melanophage/macrophage infiltration may act as a deterrent to the extension of LM along the dermo-epidermal junction of surrounding clinically unaffected skin.

Our results are obviously limited by the small sample size and the number of variables analysed. However, they are based on a prospectively designed study with a rigorous collection of data.

In conclusion, the absence of melanophages in LM/LMM could be a marker of greater subclinical spread. Should this finding be confirmed in further studies and evaluated preoperatively (e.g. in the partial diagnostic biopsy or with *in vivo* reflectance confocal microscopy), it could be used to define the width of surgical margins required to excise them completely.