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

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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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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 a principal 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, AnaptemBio, 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, AnaptemBio, 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. Taieb has been a consultant or investigator for Pierre Fabre, Galderma, Novartis, Johnson and Johnson, Incyte, Abbvie, Modilac, Pfizer, Lilly, Arena, Biderma, 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’Oreal, has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, Incyte, Lilly, Abbvie and Novartis, has lectured at educational events sponsored by Sanofi-Genzyme, Regeneron, LEO Pharma, Abbvie and Galderma, and is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of atopic dermatitis. Dr. Trzeciak has been a speaker, consultant, investigator or advisory board member for LEO Pharma, Pierre Fabre, Pfizer, La Roche Posay, Sanofi Genzyme, Novartis, Biederma, Mead Johnson. Dr. Cork is an Investigator and/or consultant Consultant for Regeneron, Sanofi Genzyme, Pfizer, LEO, Galapagos, Novartis, Boots, L’Oreal, Reckitt Benckiser, Oxagen, Johnson&Johnson, Hyphens, Kymab, Astellas, Galderma, Procter&Gamble, Abbvie, Lilly, Galderma, Menlo, Perrigo. Dr Paul has received grants and been a consultant for Allmiral, Amgen, Abbvie, Boehringer, Celgene, Eli Lilly & Co, Novartis, Janssen, Pfizer, LEO Pharma, Merck, UCB pharma, Pierre Fabre, Regeneron, Sanofi-Genzyme. Dr Flohr is chief investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a principal investigator in the European Union Horizon 2020-funded BIOMAP Consortium (http://www.biomap-im.eu/). His department has also received investigator-led funding from Sanofi-Genzyme. 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Dr. Gelmetti has acted as advisor and/or participant in clinical trials for Bayer, Sanofi/Regeneron, Galderma and has lectured at educational events sponsored by Pfizer and Leo Pharma. Dr Szalai has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, Novartis, and has lectured at educational events sponsored by Nutricia, is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. Dr. von Kobyletzki has been an investigator, speaker, or consultant for Pfizer, Sanofi, LeoPharma and Eli Lilly. Dr. De Raeye is a consultant, member of scientific advisory boards and/ or received personal fees and non-financial support from LEO Pharma, Pierre Fabre, Sanofi-Genzyme and Biderma. Dr. Fölster-Holst reports being
consultant/Advisor for Beiersdorf AG, Johnson&Johnson, LEO Pharma, Neubourg, Novartis Pharma AG, Nutricia, Pfizer Inc., Regeneron, Sanofi-Aventis as well as speaker for Beiersdorf AG, LEO Pharma, Neubourg, Novartis Pharma AG, Pierre Fabre Laboratories, Pfizer, Procter&Gamble, Regeneron, Sanofi-Aventis. Dr Christen-Zaechs has been an advisor, speaker or investigator for Galderma, L'Oreal, La Roche Posey, Pierre Fabre, Procter and Gamble and Sanofi-Genzyme. Dr. Hijnen has been investigator, speaker, or consultant for Abbvie, Eli Lilly, Incyte, LeoPharma, MedImmune/Astrazeneca, Pfizer, Sanofi, ThermoFisher. Dr. Gieler has received institutional research grants from Galderma, has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, Lilly, Abbvie and Novartis, has lectured at educational events sponsored by Sanofi-Genzyme, Abbvie, Novartis, Sebamed and Galderma, and is involved in the organization of atopic dermatitis education programs in Germany for the treatment of atopic dermatitis. Dr. Bangert has been a consultant or speaker for Bayer, Mylan, LEO Pharma, Pfizer, Sanofi Genzyme, Eli Lilly, Novartis, Celgene and AbbVie and principal investigator for Merck, Novartis, Sanofi, Abbvie, Eli Lilly, and Galderma. Dr. Spuls has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received departmental independent research grants from pharmaceutical industries different since December 2019 for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigator of the SECURE-AD registry. Dr. Wollenberg has been a principal investigator, advisory board member, or consultant for AbbVie, Almirall, Galderma, Hans Karrer, LEO Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme, and received speaking honoraria from Chugai, Galderma, LEO Pharma, Lilly, Loreal, MedImmune, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. Dr. Deleuran has been a principal investigator, speaker, advisory board member, or consultant for LEO Pharma, AbbVie, Almirall, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and Pierre Fabre. This research was performed independently through the authors’ academic university and hospital affiliations.

J. Ring,1* M. Worm,2 A. Wollenberg,3 J.P. Thyssen,4 T. Jakob,5 L. Klimk,6 C. Bangert,7 S. Barbarot,8 T. Bieber,9 M.S. de Bruin-Weller,10 P.V. Chernyshov,11 S. Christen-Zaech,12 M. Cork,13 U. Darsow,1 C. Flohr,14 R. Föster-Holst,15 C. Gelmetti,16 U. Gieler,9 J. Gutermann,17 A. Heratizadeh,18 D.J. Hijnen,19 L.B. vonKobyletzki,20,21 B. Kunz,22 C. Paul,23 L. De Raeve,17 J. Seneschal,24 D. Simon,25 P.I. Spuls,26 J.F. Stalder,8 A. Svensson,27 Z. Szalai,28 A. Taieb,24 A. Torrelo,29 M. Trzeciak,30 C. Vestergaard,31 T. Werfel,18 S. Weidinger,18 M. Deleuran31

1Department Dermatology Allergy Biederstein, Technical University Munich, Munich, Germany, 2Division Allergy and Immunology, Department of Dermatology and Allergology, Charité University Hospital, Berlin, Germany, 3Department of Dermatology and Allergology, Ludwig Maximilian University Munich, Munich, Germany, 4Department of Dermatology and Venerology, Bielefeld Hospital, Bielefeld, Germany, 5Allergy Center Wiesbaden, Wiesbaden, Germany, 6Department of Dermatology University, Vienna, Austria, 7Department of Dermatology, Nantes University, CHU Nantes UMR 1280 PhAN, INRAE, Nantes, France, 8Department of Dermatology and Allergy, University of Bonn, Bonn, Germany, 9National Expertise Center of Atopic Dermatitis, Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands, 10Department of Dermatology and Venerology, National Medical University, Kiev, Ukraine, 11Pediatric Dermatology Unit, Departments of Dermatology and Pediatrics, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, 12Sheffield Dermatology Research. Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, UK, 13St John’s Institute of Dermatology, King’s College London and Guy’s & St Thomas’ NHS Foundation Trust, London, UK, 14Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Venerology and Allergology, Kiel, Germany, 15Unit of Pediatric Dermatology, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, 16Department of Dermatology, Universitätsklinikum Ziekenhuis Brussel (UZB), Free University of Brussels (VUB), Brussels, Belgium, 17Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany, 18Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, 19Faculty of Medicine, University Healthcare Research Center, Lund University, Lund, Sweden, 20Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö, Sweden, 21Dermatologikum Hamburg, Hamburg, Germany, 22Department of Dermatology, Toulouse University, Toulouse, France, 23Department of Adult and Pediatric Dermatology, CHU Bordeaux, University of Bordeaux, Bordeaux, France, 24Department of Dermatology, Inselspital, Bern University Hospital, Bern, Switzerland, 25Department of Dermatology, Amsterdam Public Health/Infection and Immunology, Location AMC, Amsterdam, The Netherlands, 26Department of Dermatology, Skane University Hospital, Malmö, Sweden, 27Department of Dermatology of Heim, Pål National Children’s Institute Budapest, Budapest, Hungary, 28Department of Dermatology, Hospital Infantil Niño Jesús, Madrid, Spain, 29Department of Dermatology, Venereology and Allergology Medical, University of Gdansk, Gdansk, Poland, 30Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

*Correspondence: J. Ring. E-mail: johannes.ring@tum.de

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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 phenotype III–IV,5 incompletely excised or recurrent tumours,1,4 history of previous treatment,6 nests formation,5 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 treated with stage 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.