Epitope competition and neutralizing antidrug antibodies: immune monitoring of antiprogrammed death-1 therapies and lessons learned from natalizumab

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Dear Editor, We read with interest the article in the *BJD* by Gambichler and colleagues[1] about a decline of programmed death (PD)-1^+ circulating T regulatory cells (Tregs) predicting clinical outcome in anti-PD-1 therapy. The study highlights the potential and importance of immune monitoring in anti-PD-1 checkpoint therapy in malignant melanoma.

However, their conclusion about anti-PD-1 antibody treatment effecting a decline of PD-1^+ Tregs is misleading. A decline of a cell population infers 'disappearance', which normally is not the effect of therapeutic blocking antibodies. Their IgG4 backbones save target cells from antibody and/or complement-dependent cell-mediated cytotoxicity and depletion from circulation. The reported 'decrease' of $CD4^+$ $CD25^{++}$ $CD127^-$ PD-1^+ T cells thus lacks acknowledging that cell-bound therapeutic anti-PD-1 antibodies may simply interfere with detection by anti-PD1 detection antibodies due to 'steric hindrance'. In fact, it is well established that therapeutic and several clones of detection anti-PD1 antibodies compete for the same epitope.[2,3]

Differentiating a 'decrease' from 'not detectable' is important because blocking effects are reversible as soon as trough plasma levels of therapeutic antibodies subside. This implicates possible disease reactivation following treatment discontinuation but also the opportunity to accelerate a washout of the therapeutic antibody if needed. We learned this from natalizumab, an alpha-4 integrin blocking antibody used for the treatment of multiple sclerosis, where discontinuation turned out to be a major problem associated with alpha-4 re-expression dynamics. In contrast, in the case of a rare but fatal treatment complication due to John Cunningham virus reactivation, an accelerated natalizumab washout by plasma exchange allowed a hurrying up of re-expression of alpha-4 for re-establishing immune competence.[4]

The question remains as to whether the extent of PD-1 expression is not detectable because of bound therapeutic antibody or because of a true decrease in the form of shedding or internalization of receptor-antibody complexes. Of note, Zelba and colleagues already approached this question and developed a flow cytometry method for quantifying PD-1-expressing T cells including the detection of cell-bound therapeutic antibodies with antihuman IgG4 detection antibodies.[3]

Our second point concerns the patient highlighted in Figure 1 in the article by Gambichler *et al.*,[1] showing a paradoxical increase of PD-1^+ Treg frequencies under anti-PD-1 therapy. This astonishing observation raises the question of an increased drug-antibody turnover, possibly due to the presence of anti-PD-1 neutralizing antibodies. According to the European Medicines Agency/European Public Assessment Report product information for Opdivo and Keytruda,[5,6] antidrug antibodies occurred in 11% of 2022 nivolumab-treated patients, with neutralizing antidrug antibodies in 0·7% patients, and in 2% of 2034 pembrolizumab-treated patients with neutralizing antidrug antibodies in 0·4%.

Although rare, anti-PD-1 neutralizing antibodies occur and may contribute to treatment resistance. From earlier studies in multiple sclerosis we know that natalizumab neutralizing antibodies can occur after the first infusion and, importantly, can clear circulating therapeutic antibodies within a few days post infusion.[7]

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References

1 Gambichler T, Schröter U, Höxtermann S *et al.* Decline of programmed death-1-positive circulating T regulatory cells predicts more favourable clinical outcome of patients with melanoma under immune checkpoint blockade. *Br J Dermatol*; 2020; **182**:1214–20.
2 Ribas A, Shin DS, Zaretsky J *et al.* PD-1 blockade expands intratumoral memory T cells. *Cancer Immunol Res* 2016; **4**:194–203.
3 Zelba H, Bochem J, Pawelec G *et al.* Accurate quantification of T-cells expressing PD-1 in patients on anti-PD-1 immunotherapy. *Cancer Immunol Immunother* 2018; **67**:1845–51.
4 Khatri BO, Man S, Giovannoni G *et al.* Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology* 2009; **72**:402–9.
5 Opdivo production information. Available at: www.ema.europe.eu>opdivo-epar-product-information_en (last accessed 6 April 2020).
6 Keytruda production information. Available at: www.ema.europa.eu>keytruda-epar-product-information_en (last accessed 6 April 2020).
7 Pilz G, Harrer A, Oppermann K *et al.* Molecular evidence of transient therapeutic effectiveness of natalizumab despite high-titre neutralizing antibodies. *Mult Scler* 2012; **18**:506–9.

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Global reporting of cases of COVID-19 in psoriasis and atopic dermatitis: an opportunity to inform care during a pandemic

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Dear Editor, We wish to bring your attention to the PsoProtect (Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of Covid-19 infecTion) and SECURE-AD (Surveillance Epidemiology of Coronavirus Under Research Exclusion – Atopic Dermatitis) registries, two urgent global initiatives that address an unmet need for delineating the determinants of coronavirus disease 2019 (COVID-19) outcomes in the

common cutaneous immune-mediated inflammatory diseases (IMIDs) psoriasis and atopic dermatitis.

The highly transmissible COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created an unprecedented global public health emergency. The pandemic has placed an immense strain on healthcare systems and societal infrastructure worldwide. Most patients exhibit mild-to-moderate symptoms and recover without sequelae; however, around 15% develop severe pneumonia, and 5% progress to acute respiratory distress syndrome, septic shock and/or multiple organ failure, associated with high mortality.[1] There is an urgent need to better delineate the risk factors leading to poorer outcomes, with emerging data suggesting the elderly and those with pre-existing comorbid conditions such as cardiovascular disease, poorly controlled asthma and diabetes are at highest risk.[2]

Although the precise mechanisms by which SARS-CoV-2 causes severe illness are not known, exaggerated innate inflammatory and impaired adaptive immune responses have been observed.[1] Given the immunopathogenesis and treatment paradigm of IMIDs, this group of conditions poses a particular management challenge in the pandemic, and also a potential opportunity to gain insight into the host immune response to the virus.

Both psoriasis and atopic dermatitis are associated with multimorbidity and typified by innate and adaptive immune dysregulation, which is targeted by immunomodulatory therapies.[3,4] In the context of COVID-19, the broad immune suppression conferred by conventional systemic agents, such as methotrexate, may downregulate protective host antiviral immune responses. On the other hand, should treatment need to be paused in the pandemic, the longer half-life and particular pharmacokinetics of biological therapies will limit the speed of their systemic clearance. Although real-world observational data suggest an increased risk of serious infections with some agents,[5,6] their relative safety in relation to COVID-19 is unknown.[7] Conversely, there is a theoretical protective role of immunomodulators in attenuating a severe systemic inflammatory response to infection. JAK inhibitors (which have demonstrated efficacy in psoriasis and atopic dermatitis in clinical trials) and interleukin-1 inhibitors are being explored as treatments for COVID-19.[8] Finally, genome-wide association studies have uncovered a potential pathogenic role for upregulated innate antiviral immune responses in psoriasis;[3] however, it is unclear whether this has implications for risk or outcome of COVID-19.

To address these gaps, the international clinical, scientific and public health dermatological communities rapidly connected, with the common aim of gathering observational data on COVID-19 outcomes in psoriasis and atopic dermatitis on a global scale. PsoProtect (www.psoprotect.org) and SECURE-AD (www.covidderm.org) are web-based registries for clinicians to report COVID-19 outcomes in psoriasis and atopic dermatitis, respectively. They have received robust support from international dermatological professional and patient organizations, and wide participation of clinicians is now vital.

Clinicians worldwide are invited to complete the short web-based PsoProtect and SECURE-AD case report forms for any cases of confirmed or suspected COVID-19 in psoriasis and atopic dermatitis. The forms collect patient demographics, comorbidities, change in psoriasis/atopic dermatitis severity during COVID-19, immunomodulator medications (including drug exposure prior to/during the illness), and COVID-19 symptoms, management and outcome. The rapid adoption of virtual care models in the current pandemic has transformed the landscape of dermatological practice and is highly conducive to reporting cases in PsoProtect and SECURE-AD. Data are collected online and processed solely for the purpose of medical research undertaken in the public interest. No patient identifiers are collected.

The accumulating prospective observational clinical datasets in PsoProtect and SECURE-AD, alongside emerging data in the scientific literature, may help to guide clinical decision making during the pandemic. A key objective is to identify predictors (e.g. immunomodulator medications, comorbidities, demographic variables) of COVID-19 outcomes in psoriasis and atopic dermatitis, and to characterize patients in whom it may be beneficial to pause, continue or initiate systemic treatment. Regular open-access summaries of aggregated data will be published online for the benefit of the global clinical and patient community. Researchers are also actively encouraged to apply to utilize the registry data.

Importantly, these data may generate hypotheses on the underlying immunological basis for COVID-19 outcomes, which may inform the development of life-saving treatments and vaccines. The scientific basis and mode of action of immunomodulators in psoriasis and atopic dermatitis has been rigorously evaluated,[3,4] so any emerging novel associations of these therapies or disease-specific characteristics with COVID-19 outcomes may provide insight into pathomechanisms of the infection beyond these conditions and dermatology.

Subsets of patients will be compared to determine the impacts on COVID-19 outcomes of specific immunomodulators/drug classes, disease severity and demographic variables such as age, sex, ethnicity and geographical regions. Cross-IMID comparisons are also important, as individual diseases may confer differential risks on COVID-19 outcome. The data fields in PsoProtect and SECURE-AD case report forms are therefore aligned with those of similar global efforts in rheumatology (https://rheum-covid.org/) and inflammatory bowel disease (https://covidibd.org/). Because treatments such as tumour necrosis factor-α antagonists are shared across IMIDs, greater power to infer impact of specific immunomodulators on outcomes may be afforded by combining disease datasets.

Any preliminary data should be interpreted with caution, particularly where case numbers are limited. An observational design is necessary for the capture of real-world outcomes in the registries; however, there is inevitable potential for bias and incomplete data capture. For instance, clinicians may be more likely to report, and in more severe/complex skin disease, in better resourced health-care systems. In the context of a global case collection, cross-national differences in public health strategies will also need to be accounted for when interpreting outcome data.

A limitation of registries relying on spontaneous reporting is a lack of denominator data for each treatment. To help to mitigate this, data from PsoProtect and SECURE-AD can be used to enrich existing large-scale pharmacovigilance registries. Subsequent meta-analyses may give more precise estimates of the risks associated with each drug/variable.

Patient-reported outcomes of COVID-19, patient experiences and health behaviours during the pandemic are also key considerations for informing clinical care. Therefore, patient-led collections of data will be pursued, with the data fields of the patient case report forms closely matched to those of PsoProtect and SECURE-AD. This will enable inclusion of individuals with milder psoriasis and atopic dermatitis, and also less severe COVID-19 infections, reducing the risk of selection bias.

In conclusion, close international collaboration between clinicians, scientists and patients in the current pandemic is essential to fulfil PsoProtect and SECURE-AD's exciting potential to rapidly accrue large-scale datasets with high translational value. The knowledge gained from these efforts will be vital for guiding treatment choices and counselling patients on how to mitigate the potential risk of COVID-19.

Please help to inform our common clinical practice in the coming weeks and months by reporting your cases of COVID-19 today.

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References

1 Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 2020; **20**:269–70.
2 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**:1239–42.
3 Mahil SK, Capon F, Barker JN. Update on psoriasis immunopathogenesis and targeted immunotherapy. *Semin Immunopathol* 2016; **38**:11–27.
4 Weidinger S, Beck LA, Bieber T *et al.* Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**:1.
5 Kalb RE, Fiorentino DF, Lebwohl MG *et al.* Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatol* 2015; **151**:61–9.
6 Schneeweiss MC, Perez-Chada L, Merola JF. Comparative safety of systemic immuno-modulatory medications in adults with atopic dermatitis. *J Am Acad Dermatol* 2019; https://doi.org/10.1016/j.jaad.2019.05.073
7 Wollenberg A, Flohr C, Simon D *et al.* European Task Force on Atopic Dermatitis (ETFAD) statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2)-infection and atopic dermatitis. *J Eur Acad Dermatol Venereol* 2020; https://doi.org/10.1111/jdv.16411
8 Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis* 2020; https://doi.org/10.1016/s1473-3099(20)30262-0

Funding sources and conflicts of interest can be found in Appendix S1 (see Supporting Information).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Funding sources and conflicts of interest statements.

The interaction between filaggrin mutations and hard domestic water and the risk of early-onset atopic dermatitis

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Linked Article: Jabbar-Lopez *et al.* *Br J Dermatol* 2020; **183**:285–293.

Dear Editor, We read with interest the article by Jabbar-Lopez *et al.*,[1] showing a significant interaction between filaggrin gene