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Reply to: "Herpes zoster seven days after SARS-CoV-2 vaccination in a patient with ankylosing spondylitis under adalimumab" by Josef Finsterer

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Dear Editor,
we thank Professor Josef Finsterer for his remarks and observations on our manuscript reporting a case of cutaneous herpes zoster (HZ) following the first dose of an mRNA COVID-19 vaccine in a 41-year old female with ankylosing spondylitis (AS) under adalimumab (1).

The first concern, related to the lack of a proven causal relationship between vaccination and the development of HZ, is undoubtedly reasonable. Varicella-zoster virus (VZV) reactivation is known to occur when immunological mechanisms that suppress VZV replication fail to contain the virus, as mainly occurs in cases of HIV/AIDS immunosuppression or malignant neoplasms, as shown in a recent meta-analysis (2). Family or personal history of HZ, physical trauma, and older age were also significantly correlated with an increased risk of reactivation, while rheumatoid arthritis, systemic lupus erythematosus, kidney disease, cardiovascular disease and inflammatory bowel diseases were found to be slightly less risky factors than the previous ones (3). However, none of the significant risk factors listed above were present in our patient, including malignancy and HIV. Furthermore, the patient did not experience any SARS-CoV2 infection, nor any contact with persons known to be infected with SARS-CoV2 or other infective diseases. The only potential risk factor could actually be represented in our patient by the immunosuppressive biological treatment with adalimumab, since anti-TNF inhibitors predispose to a greater risk of HZ (4), as also appropriately highlighted by Professor Finsterer (5, 6). However, our patient had been taking adalimumab for 3 years, during which time no HZ event occurred. It therefore seems more plausible to hypothesize that the vaccine could represent the trigger event for the appearance of HZ rather than adalimumab itself.

Moreover, according to recent studies, postherpetic neuralgia secondary to HZ reactivation may potentially be increased by cell-mediated immunity disfunction due to elevated oxidative stress status, as well as elevated inflammatory mediators, such as IL-6 and IL-18 (7, 8). The synergistic effect of increased oxidative status and pro-inflammatory cytokines production eventually lead to imbalance in immune and inflammatory response; according to these findings biological therapy may affect this synergy, while reducing inflammation. Further reports are fundamental to clarify this point. Therefore, as we stated in our manuscript, although it is not possible to establish a straightforward relationship between the occurrence of VZV reactivation and COVID-19 vaccination, the hypothesis appears plausible.

Standard algorithms have been developed by the World Health Organization (WHO) to conduct causality assessments of individual cases of adverse events following immunization (AEFI). '*Consistent with a causal relationship*' means a temporal relationship with proven evidence for increased risk. Likewise, a '*probable association*'

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designate a temporal relationship but in the absence of a strong explanation for a biologic mechanism of causal association between the vaccine and the event (9).

In our case, the close temporal association between VZV reactivation and vaccination (1-21 days after the priming dose) supports the AEFI as being '*consistent with*', while the cases described hitherto in literature (10) may reflect the existence of a plausible biologic mechanism, supporting a '*probable*' causal association based on the WHO Working Group. We feel that the increasing number of immunosuppressed individuals worldwide and the recent interest in the vaccination issue (11, 12), in light of the novelty of SARS-CoV-2 vaccination, makes our case report worthwhile.

Another point regards polymerase chain reaction (PCR) demonstration of infection. This testing is usually not necessary to diagnose an active infection, because it can be diagnosed clinically. PCR is desirable only when acute diagnostic confirmation is needed, mainly in patients with atypical skin lesions. As reported in our manuscript, since the dermatological skin rash was found consistent for HZ by the GP, PCR has not been performed initially to accelerate the start of antiviral therapy, and when the patient presented to our Rheumatologic Clinic, because the high probability of a negative test result, after one week of antiviral therapy.

Additionally, several guidelines suggest investigating the incidence and prevalence of vaccine-preventable infections in adult patients with autoimmune or inflammatory diseases; consequently, the effect and safety issues of vaccination are under careful examination (11). Moreover, immunosuppression and immunodeficiency were contraindications for the previously available vaccine in the past years, thus live zoster vaccine was originally recommended for immunocompetent adults aged ≥50 years, leading to an unmet need for vaccination against HZ in immunocompromised adults. Only in 2021, the Food and Drug Administration (FDA) expanded the indication for recombinant zoster vaccine to include adults aged ≥18 years who are or will be at increased risk for HZ because of immunodeficiency or immunosuppression caused by diseases or therapies (13, 14). Therefore, recent debate and attention inevitably focused on VZV reactivation, questioning on the available vaccines in preventing HZ complications, which lead to healthcare resource utilization and healthcare associated costs (15-18).

In conclusion, considering all these efforts and the current pandemic challenge, we believe that now more than ever we are asked to quickly detect potential adverse events, even extremely rare and mild ones, and to face them, in order to support the robust pharmacovigilance campaign for SARS-CoV2 vaccination (19, 20).

Conflict of interest

The authors declare no potential conflict of interest.

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