the novel analytical methods currently introduced for evaluation of real-world data and patient-level data acceptable for regulators and other decision makers, testing and validation should be performed in broadly the same way as for RCTs.[3] On the other hand, scientific journals still seem to be sceptical about the scientific value and suitability for publication of real-world data without a specialized expert review process.[4] Interestingly, real-world data have already been used by the EMA to approve several medicines for rare or orphan indications.[1]

HS is exactly such a disease, for which RCTs may have excluded, up to now, a considerable number of patients such as those with very severe disease, patients with no scarring component at baseline, patients with considerable comorbid conditions, such as cardiovascular abnormalities,[5] and patients previously treated with registered drugs of a similar pharmacochemical group. In an effort to close this gap, as reported in this issue of the *BJD*, Marzano *et al.* present their results of a retrospective and observational study with 389 patients with HS treated with adalimumab in 21 Italian centres in a real-world setting.[6] Fulfilment of Hidradenitis Suppurativa Clinical Response (HiSCR) under adalimumab treatment was achieved by 170 patients (43.7%) at week 16, a result similar to that of the adalimumab registration studies PIONEER I (41.8% at week 12) and PIONEER II (58.9% at week 12).[7] Moreover, the overall safety profile of adalimumab was excellent, with only mild reported adverse events, including transient asthenia, headache and nausea. Adalimumab discontinuation occurred in 14.9% of patients, mainly due to lack or loss of efficacy, a rate that is markedly higher than that in the PIONEER I and II studies (18 of 315, 5.7%).[7]

Interestingly, the 'therapeutic delay' correlated to lack of response to adalimumab at week 16 and was detected as a reliable parameter, predicting the clinical response to adalimumab in HS. Furthermore, inclusion criteria for RCTs up to now have included presence of a scarring component, so patients with Hurley stage I have been excluded. The use of validated outcomes for baseline severity, such as the International Hidradenitis Suppurativa Severity Score System (IHS4), which was used by Marzano *et al.*, suggests that definition of moderate and severe disease does not require the presence of a scarring component, as Hurley staging suggests.

The outcome of the study, together with the inverse correlation of achieved HiSCR with previous immunosuppressant treatment, provides evidence for a 'window of opportunity' suggesting that administration of adalimumab in early phases of HS should be highly encouraged. This also contradicts the registration of adalimumab as a second-line treatment after failure to respond to conventional systemic treatments (e.g. systemic antibiotics). Furthermore, this evidence provides a clear indication that the use of validates outcomes, such as IHS4, for defining the entry point to an RCT may be of substantial benefit. The proposed diversified procedure might reduce work loss, as well as direct and indirect costs of HS treatment.[8]

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Impaired type I interferon response in SARS-CoV-2 infection: looking through the cutaneous window

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Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, strong evidence has accumulated for the key

role of an inappropriate, insufficient, overactive and/or delayed type I (mainly alpha and beta) interferon response during SARS-CoV-2 infection. Most studies have concerned critically ill patients with COVID-19 and the results have been discrepant and even contradictory. This likely reflects differences in the criteria of the studies, such as timing of sampling, nature of the affected organs, severity of the disease and presence of comorbidities.[1–4]

To date, about 1500 cases of chilblain-like (perniosis-like) skin lesions have been reported during SARS-CoV-2 infection (initially referred to as 'COVID toes'), with the following data highlighted: elective occurrence in young adults, milder disease spontaneously resolving, and low rate of positivity to SARS-CoV-2 nasopharyngeal polymerase chain reaction (PCR) or blood serology. More recently, a causative role of SARS-CoV-2 in this outbreak of chilblain-like lesions (since named COVID-19 chilblains) was confirmed by the immunohistochemical and ultrastructural identification of direct viral infection in the endothelial cells of the upper dermal vessels and the epithelial cells of eccrine glands.[5] The clinical and histopathological similarities of COVID-19 chilblains to the acral cutaneous lesions observed in genetic interferonopathies, notably familial chilblain lupus and STING-associated vasculopathy with onset in infancy (SAVI),[6] suggest a pivotal pathogenic role of upregulation of type I interferon response in causing these skin lesions. These data have prompted the hypothesis of a pathophysiological mechanism of COVID-19 chilblains that can be summarized as follows: high production of type I interferon at the onset of viral infection – perhaps a hallmark in children, young adults and predisposed patients – is associated with the early and rapid inhibition of the replication and clearance of the virus, accounting for the mild disease course, the usually negative PCR test positivity and the negativity of serologies.[7,8]

In this issue of the *BJD*, Magro and colleagues compared the histopathological and immunohistochemical staining of SARS-CoV-2 protein and RNA and the cytokine features in a short series of idiopathic perniosis, COVID-19 chilblains and retiform purpura of severe or critically ill patients with COVID.[9] They thus confirmed the marked separation in the histological pattern of the two cutaneous manifestations of COVID-19. COVID-19 chilblains comprise a highly lymphocytic inflammatory process with a type I interferon-enriched microenvironment, as evidenced by extensive epidermal and dermal expression of MxA and rich presence of plasmacytoid dendritic cells, and minimal vascular injury in COVID-19 chilblains. On the other hand, COVID retiform purpura reveals a pauci-inflammatory thrombotic complement-driven microvascular injury syndrome. In the latter case, microscopic and immunohistological findings were strikingly similar to the septal capillary injury observed in pulmonary autopsy samples of patients who died of acute respiratory distress syndrome, suggesting a common pathophysiological mechanism.[10] The study also highlights the quantitative and anatomical variations of viral protein expression: mild and mostly in inflammatory cells in COVID-19 chilblains, and extensive and endothelial in COVID retiform purpura.

In summary, Magro and colleagues provide further indirect confirmation of the key role of an impaired type I interferon response in SARS-CoV-2 infection during COVID-19 chilblains and retiform purpura by skin immunophenotyping. Nevertheless, additional longitudinal studies of type I interferon signatures in peripheral white blood cells and lesional skin are needed to provide direct evidence of this concept.

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