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Variant *STAT4* and Treatment of an Autoinflammatory Syndrome

TO THE EDITOR: We describe the case of a 21-year-old man who died from an intractable disabling panssclerotic morphea (DPM). The disease began when he was 12 years of age and manifested as localized morphea with multiple oval, shiny, and thickened lesions.

At 16 years of age, severe erosive ulcers developed on his hands, feet, and legs, resulting in a highly disabling form of DPM (Fig. 1). During the subsequent years, he received several treatments: methotrexate, mycophenolate mofetil, intravenous immune globulin, rituximab, iloprost, cyclosporine, thalidomide, cyclophosphamide, tocilizumab, bosentan, and glucocorticoid pulses, together with hyperbaric therapy and eventually mesenchymal stem-cell transplantation — all with no benefit. The patient died from sepsis with multiorgan failure in 2017.

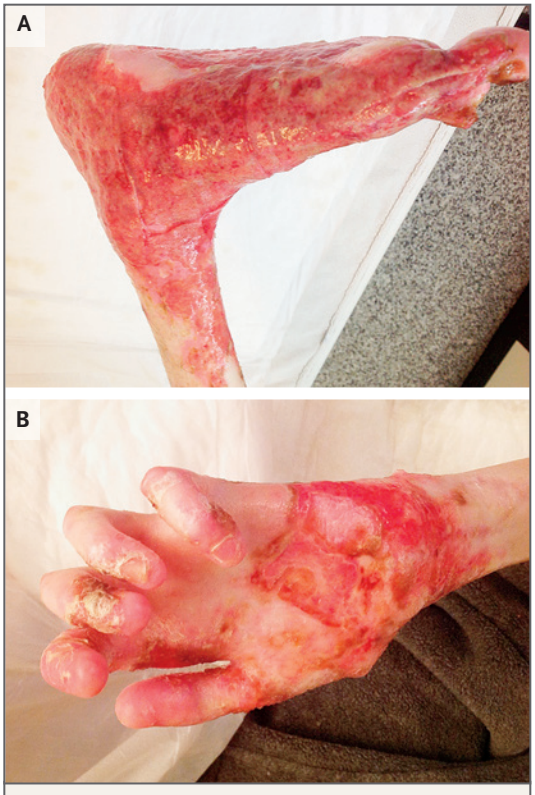

Figure 1. Ulcerations of the Foot and Hand.

The article by Baghdassarian et al. (June 15 issue)[1] underlined the role of hyperactive signal transducer and activator of transcription 4 (STAT4) in clinical manifestations of DPM and suggested a possible use of Janus kinase (JAK) inhibitors "for patients in the most severely affected family" with refractory disease. However, we believe that JAK inhibitors must be considered early when the disease takes a panssclerotic course because it can rapidly lead to a fatal outcome despite conventional treatments.[2]

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THE AUTHORS REPLY: We agree with Pastore et al. that an immunomodulatory approach with JAK inhibitors may be effective for patients with disabling panssclerotic morphea (DPM) and refractory disease. Early intervention is key for reducing complications across the spectrum of autoinflammatory disease,[1,2] and we hypothesize that if JAK inhibitors had been available at the onset of disease for the other patients with DPM

described in our article, their disease courses might have been different in that amputation might have been prevented or mortality reduced. Although JAK inhibitors are not currently approved by the Food and Drug Administration or the European Medicines Agency for the treatment of DPM, we agree that this expanding class of pharmaceutical agents offers opportunities for targeted therapy.[3,4] As more patients with DPM and more mutations in *STAT4* or related pathways are identified, we predict that we will see the evolution of molecularly defined subsets of disease. Increased recognition through sharing of both clinical descriptions and multi-omic descriptions (i.e., involving multiple "omes," such as the genome and transcriptome) of patients with this rare and challenging condition may help to delineate the choice of therapy early in the disease course for individual patients.

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Since publication of their article, the authors report no further potential conflict of interest.

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Axicabtagene Ciloleucel in Large B-Cell Lymphoma

TO THE EDITOR: The ZUMA-7 trial showed breakthrough progress in the treatment of early relapsed or refractory large B-cell lymphoma. However, Westin et al. (July 13 issue)[1] listed limitations such as the low proportion of non-Hispanic patients, restricted eligibility as compared with the real-world distribution of the disease, and the absence of patients who were ineligible for autologous stem-cell transplantation.

We can provide evidence from the China pivotal study[2] and a real-world study[3] of axicabtagene ciloleucel (axi-cel), which together included 73 patients who had relapsed or refractory large B-cell lymphoma as defined in the ZUMA-7 trial. At a median follow-up of 9.3 months, 58 of the 73 patients (79%) had an objective response to treatment (i.e., a complete or partial response), and 40 (55%) had a complete response as their best response. Median overall survival was 24.8 months. Grade 3 or higher cytokine release syndrome occurred in 11% of the patients, and grade 3 or higher neurologic adverse events occurred in 3%. Among the 28 patients in these two studies who were ineligible for autologous stem-cell transplantation (≥65 years of age, an Eastern Cooperative Oncology Group performance-status score of ≥2, or previous autologous stem-cell transplantation),[2,3] 23 (82%) had a response, and 15 (54%) had a complete response.

The effectiveness and safety of axi-cel in this real-world study involving patients with large B-cell lymphoma in Asia were similar to those in the ZUMA-7 trial.[3] Despite the different baseline characteristics between the patients in the real-world study and those in the trial, we still found that axi-cel was of benefit for patients who are ineligible for autologous stem-cell transplantation.

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