common in individuals with a lower Charlson-Deyo score ($P < .001$), private insurance ($P < .001$), treatment at an academic facility ($P < .001$), and younger individuals ($P < .001$). The percentage of patients receiving immunotherapy rapidly increased from 17.5% in 2012 to 50.2% in 2016 ($P < .001$). Notably, no difference by sex ($P = .942$) or race/ethnicity ($P = .706$) was detected.

In the multivariate regression model, immunotherapy use was associated with diagnosis after 2012, particularly 2015 (odds ratio [OR], 3.28; 95% confidence interval [CI], 2.67-4.02), $P < .001$) and 2016 (OR, 5.06; 95% CI, 4.13-6.19; $P < .001$) and residing in zip codes with the third-highest (OR, 1.36; 95% CI, 1.12-1.65; $P = .002$) or highest (OR, 1.36; 95% CI, 1.12-1.64; $P = .002$) income quartile (Table II). Factors with less frequent immunotherapy use included older age (OR, 0.97; 95% CI, 0.97-0.98; $P < .001$), residing in the southeastern United States (OR, 0.81; 95% CI, 0.69-0.95; $P = .009$); and being uninsured (OR, 0.64; 95% CI, 0.47-0.99; $P = .006$) or having Medicaid insurance status (OR, 0.61; 95% CI, 0.47-0.78; $P < .001$).

These data show that between 2012 and 2016, there has been an explosive increase in the use of immunotherapy. This is likely due to the timing of US Food and Drug Administration approvals for ipilimumab (2011) and nivolumab (2014).[5] Although the data are limited up to 2016, we suspect an increasing trend may continue with future data. Overall, immunotherapy use is greater in younger, healthier, and more affluent individuals and is lower in older individuals, individuals with comorbidities, and those receiving care at nonacademic centers.

NCDB limitations include that data are available only through 2016, as well as lack of specificity regarding an exact immunotherapy given or tumor genetics.

Although oncologists prescribe immunotherapy, dermatologists are invaluable in diagnosing and managing its cutaneous adverse events. Together, both specialties deal with the benefits and adverse effects of these new treatments. As more patients with stage 4 melanoma receive immunotherapy, dermatologists should prepare themselves to manage and discuss these adverse events with both patients and oncologists.

Parth V. Shah, BA,[a] Jennifer N. Choi, MD,[a] Lori Fiessinger, MD,[b] Beatrice Nardone, MD, PhD,[a] Cuong V. Nguyen, MD,[a] and Walter Liszewski, MD[a,c]

From the Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois[a]; Department of Dermatology, University of Minnesota, Minneapolis, Minnesota[b]; and Division of Cancer Epidemiology, Northwestern University, Chicago, Illinois.[c]

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Correspondence to: Walter Liszewski, MD, 676 N St. Clair St, Suite 1600, Chicago, IL 60610

E-mail: wjliszewski@gmail.com

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Dynamic cytokine profiles combined with enzyme-linked immunospot assay are useful for immunologically confirming the dapsone hypersensitivity syndrome

To the Editor: Dapsone hypersensitivity syndrome (DHS) is a dapsone-induced T−cell mediated delayed type of hypersensitivity, characterized by fever, rash, lymphadenopathy, and hepatic function abnormalities.[1] The diagnosis of DHS is traditionally based on the criteria proposed by Richardus and Smith.[1] However, the diagnosis remains a challenge in clinical practice due to the difficulty of distinguishing DHS from other drug-induced hypersensitivity reactions (DHRs), concurrent infections, or other underlying diseases. The enzyme-linked immunospot (ELISpot) method quantifying the release of antigen-specific cell cytokines has been widely used in diagnosis of DHR by distinguishing culprit drugs from coadministered drugs.[2]

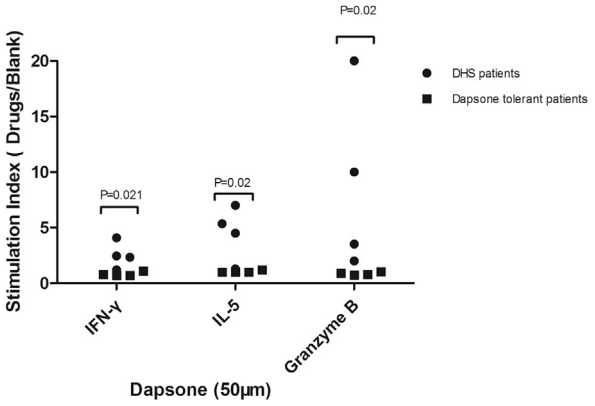

Fig 1. Comparative analysis of IFN-γ, IL-5, and granzyme B in DHS patients with DHS and dapsone-tolerant patients. The PBMCs from patients were cultured with dapsone (50μM), and secretions of IFN-γ, IL-5, and granzyme B were measured at day 6. Stimulation index (SI) is calculated by secretion of cytokines with drug/without drug (negative control). Mann-Whitney test was used for comparative analysis of SI between patients with DHS and dapsone-tolerant patients with a significant *P* value ($P < .05$).

To investigate the specific ELISpot assay for the DHS diagnosis, we performed a comprehensive analysis of dynamic cytokine profiles, analyzing 13 cytokines (interferon [IFN]-γ, Fas ligand, granzyme B, interleukin [IL] 4, IL-5, IL-6, IL-13, IL-15, IL-17A, IL-21, IL-22, IL-23, and tumor necrosis factor-α) in peripheral blood mononuclear cells stimulated with and without dapsone using Luminex (R&D Systems) assay in 4 patients with DHS and 4 patients who were dapsone tolerant.

After stimulation with dapsone, the stimulation index (SI) of patients with DHS showed higher levels of IFN-γ, IL-5, and granzyme B than the SI in patients who were dapsone tolerant at day 6 ($SI > 2$; $P < .05$) (Fig 1). We further developed ELISpot assays and applied them to examine the SI in 16 patients with DHS, 4 patients who were dapsone tolerant, 12 patients with DHR induced by other drugs, and 12 healthy donors. In 16 patients with DHS, 9 (56.25%), 11 (68.75%), and 11 (68.75%) were positive for IFN-γ, granzyme B, and IL-5 ELISpot, respectively, whereas the combination of the 3 cytokines increased the sensitivity to 87.5% (14 of 16). No patients without DHS tested positive by the ELISpot assays, presenting a 100% specificity.

The statistical power showed more than 99.9% at 5% significance calculated by the pwr package of R software (The R Foundation for Statistical Computing, Vienna, Austria). The clinical characteristics of all patients with DHS and the results of the ELISpot assays are summarized in Table I.[1] Additional information is available via Mendeley at https://data.mendeley.com/datasets/23h5s468c4/draft?a=e9b64699-14b0-464f-be69-e7fda7f38a9a.

The efficacy of ELISpot assay for the diagnosis of DHR has been previously reported.[2] However, its sensitivity varied due to the diverse pathogenesis involving in the initiation and progression of DHR. Moreover, 1 drug can elicit different types of DHR with distinct pathomechanism. For example, the pharmacologic interaction model and altered peptide repertoire model were both involved in the pathogenesis of carbamazepine-induced DHR,[3,4] and the related cytokines, granzyme B, granulysin, and perforin were used to establish the ELISpot assay with a combined sensitivity of 75%.[2] In this study, our dynamic cytokine profile analysis showed that the expression of IFN-γ, IL-5, and granzyme B were specifically upregulated in DHS, which was in accordance with the involvement of $CD4^+$ T cells and $CD8^+$ T cells in the pathogenesis of DHS.[5] The sensitivity of the ELISpot assay with the combined 3 cytokines was 87.5%, indicating it could be an attractive technique for DHS diagnosis.

In conclusion, we confirmed that the combined detection of IFN-γ, granzyme B, and IL-5 using the ELISpot assay showed a good performance in immunologically confirming DHS. The application of dynamic cytokine profiles promoted the development of ELISpot, which greatly enhanced the sensitivity of ELISpot in DHS diagnosis.

Jiabao You, MD, Lele Sun, MD, Qing Zhao, MD, PhD, Huimin Zhang, MD, Pengcheng Huai, PhD, Gongqi Yu, BS, Zhenzhen Wang, MD, Zihao Mi, PhD, Zheng Pang, PhD, Hong Liu, MD, PhD, and Furen Zhang, MD, PhD

From the Shandong Provincial Hospital for Skin Diseases & Shandong Provincial Institute of Dermatology and Venereology, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, China.

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Table I. Clinical characteristics and the results of enzyme-linked immunospot (*ELISpot*) assay of the 16 patients with dapsone hypersensitivity syndrome

				Clinical manifestation[†]				ELISpot assay				
No.	Age, y	Sex	Interval,[*] d	Fever	Generalized rash	Lymphadenopathy	Hepatic function abnormalities[‡]	Jaundice	IFN-γ	IL-5	Granzyme B	Combined
1	42	M	22	√		√	√		−	−	+	+
2	41	M	48	√	√	√	√		+	+	+	+
3	34	M	23	√	√	√	√	√	+	+	+	+
4	28	M	21	√	√		√		+	+	+	+
5	44	F	20	√	√		√		−	−	−	−
6	40	M	30	√	√		√		+	+	+	+
7	54	M	21	√	√		√		+	−	−	+
8	27	F	20	√		√	√		−	+	+	+
9	22	F	30	√	√	√	√		−	+	+	+
10	41	F	14	√	√	√	√		−	−	−	−
11	42	M	22	√	√	√	√		+	+	+	+
12	30	M	28	√	√	√	√		+	+	+	+
13	21	M	50	√	√		√		−	+	−	+
14	30	F	26	√		√	√		−	−	+	+
15	55	M	18	√	√	√	√		+	+	+	+
16	22	M	14	√	√		√		+	+	−	+
Positive, No. (%)									9 (56.25)	11 (68.75)	11 (68.75)	14 (87.5)

F, Female; *IL*, interleukin; *IFN*, interferon; *M*, male; √, the patients presented with this symptom.
*Interval, the time interval between onset of drug intake and appearance of symptoms.
[†]The dapsone hypersensitivity syndrome was diagnosed based on the criteria proposed by Richardus and Smith.[1]
[‡]Hepatic abnormalities were defined as 2× the upper limit of normal of aspartate aminotransferase or alanine aminotransferase at the fourth week or eighth week of follow-up.

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Correspondence to: Hong Liu, MD, PhD, 27397, Jingshi Rd, Jinan City, Shandong 250022, China

E-mail: hongyue2519@hotmail.com

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Comparative efficacy and safety of intralesional bleomycin relative to topical bleomycin with microneedling in the treatment of warts: A systematic review

To the Editor: Bleomycin is a chemotherapeutic agent first used in the treatment of warts as intralesional injection in the 1970s.[1] Despite evidence of its efficacy, it has not gained popularity, possibly due to worrisome adverse effects such as gangrene and Raynaud phenomenon that have been rarely reported with intralesional use.[2] However, other methods of bleomycin delivery are described, including multiple puncture, microneedling, microneedle patch, and