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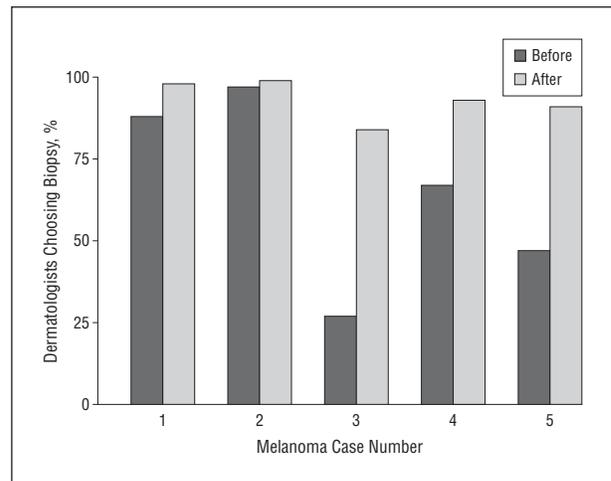
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## ONLINE FIRST

### Impact of Guidance From a Computer-Aided Multispectral Digital Skin Lesion Analysis Device on Decision to Biopsy Lesions Clinically Suggestive of Melanoma

A major challenge faced daily by clinical dermatologists is to determine which pigmented lesions are appropriate for biopsy. The present study was designed to determine the effect of guidance provided by a multispectral digital skin lesion analysis (MSDSLA) device (MelaFind; MELA Sciences Inc)<sup>1</sup> on dermatologists' decision to biopsy a pigmented lesion and the impact of the information provided by the device on the associated melanoma biopsy sensitivity and specificity. MelaFind uses light from visible to near-infrared wavelengths to image up to 2.5 mm beneath the skin and analyzes images from subbands of these wavelengths to provide information about the lesion's level of structural disorder. The device provides an output of "positive" or "negative" as an additional piece of data that can be integrated into the biopsy decision.

**Methods.** A total of 179 practicing dermatologists (median duration of practice, 11-15 years) attending an educational conference participated in an interactive melanoma session. Participants were asked to evaluate 24 pigmented lesions (5 melanomas and 19 other pigmented lesions) that had been analyzed as part of a prior study using a MSDSLA system.<sup>2</sup> To make the experi-



**Figure 1.** Percentage of study dermatologists who chose to biopsy melanomas before and after the receipt of the multispectral digital skin lesion analysis (MSDSLA) information. The overall biopsy choice of 69% before receipt of the MSDSLA information improved to 94% after information receipt.

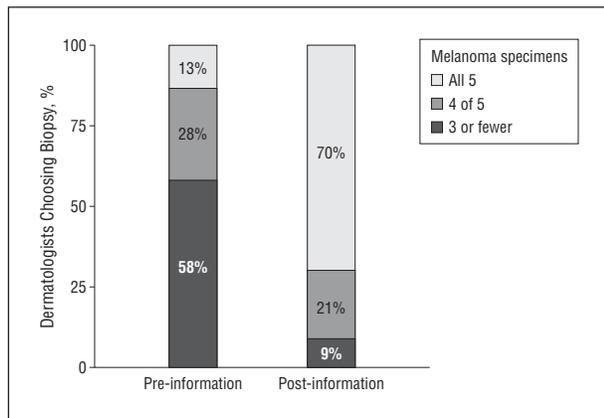
ence more clinically realistic, the lesions were grouped from 4 composite patients, each having 6 lesions, with matching historic and clinical characteristics. Patient histories were presented, and then distant and close-up clinical and dermoscopic images of each of the lesions were viewed.

Each dermatologist responded yes or no on an electronic keypad to the following question: "Would you biopsy this lesion?" Then, the MSDSLA system information was provided, and the participant responded to this question: "Would you now biopsy this lesion?" Individual responses before and after MSDSLA information were compared to determine the effect of the MSDSLA information on the biopsy decision. The study was deemed exempt by the institutional review board of New York University.

**Results.** For 179 dermatologists, the MSDSLA information improved the average biopsy sensitivity for the 5 melanomas from 69% prior to receiving the MSDSLA information to 94% after receiving the information ( $P < .001$ ) (Figure 1). Biopsy specificity declined from 54% before to 40% after MSDSLA information receipt ( $P < .001$ ). Biopsy rates of lesions that were MSDSLA negative fell from 43% before to 25% after MSDSLA information receipt ( $P < .01$ ). Of the 4 lesions that were not evaluable by the MSDSLA system, biopsy rates went from 37% before to 42% after the dermatologists learned that no MSDSLA information would be available ( $P = .16$ , showing neither a positive nor negative effect when the system provided no additional information).

Integration of the MSDSLA data into the biopsy decision process also led to a more uniform decision by the dermatologists. The multirater  $\kappa$  statistic for interobserver agreement improved from 0.32 before to 0.45 (fair to moderate) after receipt of the additional information provided from the MSDSLA system.

The changes in biopsy decisions made as a result of integrating the MSDSLA device increased the overall biopsy sensitivity with a concomitant lesser decrease in over-



**Figure 2.** Effect of multispectral digital skin lesion analysis (MSDSLA) information on biopsy decision for melanoma. Choice to biopsy all 5 of the melanomas rose from 13% of the dermatologists before MSDSLA information receipt to 70% after information receipt.

all biopsy specificity that was related in part to the fact that the device had identified as positive for biopsy some lesions that were not melanomas. However, for MSDSLA-negative lesions that were also histologically negative, the specificity increased. The overall impact of the intervention resulted in the number of potentially unnecessary biopsies being reduced by 17%.

**Comment.** Melanoma biopsy sensitivity for dermatologists has been demonstrated to consistently be in the range of 70% to 80%.<sup>3-6</sup> Therefore, there is an opportunity for computer-aided devices to improve selection accuracy for biopsying pigmented lesions. A prior prospective study found the measured sensitivity of MelaFind to be 98.4%.<sup>2</sup>

The present study demonstrated that having MSDSLA information to integrate into the biopsy decision led to a significant improvement in biopsying melanomas (69% to 94%). As would be expected, there was also a concomitant decrease in biopsy specificity after information receipt, from 54% to 40%, indicating that a biopsy recommendation from the MSDSLA system led to an increase in the number of biopsies of nonmalignant lesions. However, in the clinical setting, the risk of making a type II error (not biopsying a lesion that is a malignant melanoma) has far more severe consequences than a type I error (biopsying a nonmalignant lesion), so that in the case of melanoma diagnosis, improvement in sensitivity was more clinically relevant than a smaller decrease in specificity. When information was lacking from the MSDSLA because 4 lesions were not evaluable for technical reasons, there was no impact on the decision to biopsy (37% before vs 42% after the dermatologists learned that no MSDSLA information would be available), nor was it detrimental.

Finally, this study also demonstrates that when the additional MSDSLA information was provided, although it was incorporated into the decision process, it was not universally followed. After receiving the MSDSLA information, 70% of the dermatologists chose to biopsy all 5 of the melanomas (**Figure 2**), and 25% of the lesions reported as negative by the device were still biopsied. These facts demonstrated that the information provided by this type of diagnostic device for pigmented

lesions was integrated into all of the other factors used in making a biopsy decision but was not “blindly” followed.

Until there is a cure for melanoma, early detection of disease remains an imperative goal to improve patient outcomes. While certainly there is no substitute for clinical judgment in assessing which lesions require further investigation, the present study suggests that having the additional information provided by a MSDSLA device can significantly impact the accuracy of the decisions made by dermatologists when determining whether a pigmented lesion should be biopsied.

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## ONLINE FIRST

### Poor Benefit/Risk Balance of Intravenous Immunoglobulins in DRESS

**D**rug reaction with eosinophilia and systemic symptoms (DRESS), sometimes called hypersensitivity syndrome, is a severe drug-induced reaction with visceral involvement and blood abnormalities associated with reactivations of viruses of the herpes family: human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV).<sup>1</sup> Our research group<sup>2</sup> recently reported that the immune response in DRESS, previously thought to be directed against drug components, is in fact mediated by tumor necrosis factor (TNF)- and interferon- $\gamma$  (INF- $\gamma$ )-secreting CD8<sup>+</sup> T lymphocytes, which are directed against previously quiescent HHVs reactivated by the drug and home to the skin and visceral organs.<sup>2</sup> Oral corticosteroid treatment is often proposed for severe DRESS, but oral corticosteroids might favor a relapsing course of the syndrome. Some researchers,<sup>3,4</sup> based on the presence of antiviral IgGs in intravenous immunoglobulins (IVIGs) and their numerous immunologic effects, have suggested that IVIGs might be effective in a few patients with DRESS, although these patients were concomitantly treated with systemic corticosteroids. The aim of the present study was to evaluate the safety and efficacy of IVIGs in patients with DRESS and to assess the evolution of immunologic and virologic parameters after treatment.

**Methods.** Ten patients with severe DRESS<sup>2</sup> were considered for enrollment in this multicenter prospective open study, which was approved by the Northwest France ethics committee and registered as NCT00505648. Six patients were ultimately enrolled. Study patients were treated with IV infusions of Tegeline (LFB Biomedicaments), 200 mg/kg/d for 5 consecutive days. The primary end point was the disappearance of fever and disease progression by day 7 after treatment and complete remission without corticosteroids by day 30. The study was prematurely stopped by the ethics committee for safety reasons. To assess the role of IVIGs on viral reactivations and immunologic parameters, blood samples were collected at baseline and at days 5 (end of IVIG treatment), 10, and 30. Viral DNA from EBV, HHV-6, HHV-7, and CMV was quantified by real-time polymerase chain reaction in patients' serum and peripheral blood mononuclear cells.<sup>2</sup>

**Results.** Six patients with severe DRESS (2 men and 4 women), mean (SD) age 58 (15) years, were included in the study (**Table**). All patients had an extensive eruption and facial swelling. According to the RegiSCAR scale,<sup>5</sup> the patients' median severity score was 7 (range, 6-7) on a scale ranging from 1 to 9, meaning that the diagnosis of DRESS was certain in all patients. Patients were treated

after a median delay of 12.5 days (range, 7-24 days) after the onset of DRESS. Two patients experienced severe malaise during the infusion, one with hypertension and the other with hypotension, and so infusion was stopped by the investigators. One patient had a pulmonary embolism at day 9.

Four patients required rescue oral corticosteroid treatment, the 2 patients with initial malaise and 2 others owing to the occurrence of hemophagocytic syndrome during the follow-up period. These 4 patients dropped out of the study, according to the study protocol (ie, rescue corticosteroid treatment). Only 1 of 6 patients achieved the primary end point. This patient was in partial remission at day 30 and achieved complete remission by day 120.

Viral reactivations were observed at baseline in all 6 cases and were still observed after treatment in 3 of the 3 cases tested (**Table**). Immunologic analyses showed a slight decrease in TNF and INF- $\gamma$  serum levels from baseline to day 30 in the 2 patients who achieved partial or complete remission with IVIG treatment alone, whereas the number of TNF- and INF- $\gamma$ -producing CD8<sup>+</sup> T lymphocytes paradoxically increased despite the regression of DRESS symptoms in these patients.

**Comments.** This study does not support a beneficial effect of IVIG treatment in patients with DRESS, since 5 of 6 patients experienced severe adverse events, and 4 patients had to be treated with oral corticosteroids because of IVIG adverse effects (n=2) or uncontrolled DRESS (n=2). This absence of beneficial effect of IVIGs is in accordance with the persistence of multiple viral reactivations after treatment, which was previously reported in a patient with DRESS treated with IVIGs,<sup>4</sup> and with the absence of significant modification of immunologic parameters in patients who did not receive oral corticosteroids. Our observations suggest that IVIGs must not be used as a single treatment in DRESS.

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