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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REFERENCES

1. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev*. 1989;60(4):267-273.
2. Porebski G, Czarnobilska E, Bosak M. Cytotoxicbased assays in delayed drug hypersensitivity reactions induced by antiepileptic drugs. *Pol Arch Med Wewn*. 2015;125(11):823-834.
3. Illing PT, Vivian JP, Dudek NL, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature*. 2012;486(7404):554-558.
4. White KD, Chung WH, Hung SI, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. *J Allergy Clin Immunol*. 2015;136(2):219-234. quiz 235.
5. Zhao Q, Alhilali K, Alzahrani A, et al. Dapsone- and nitroso dapsone-specific activation of T cells from hypersensitive patients expressing the risk allele HLA-B*13:01. *Allergy*. 2019;74(8):1533-1548.

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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

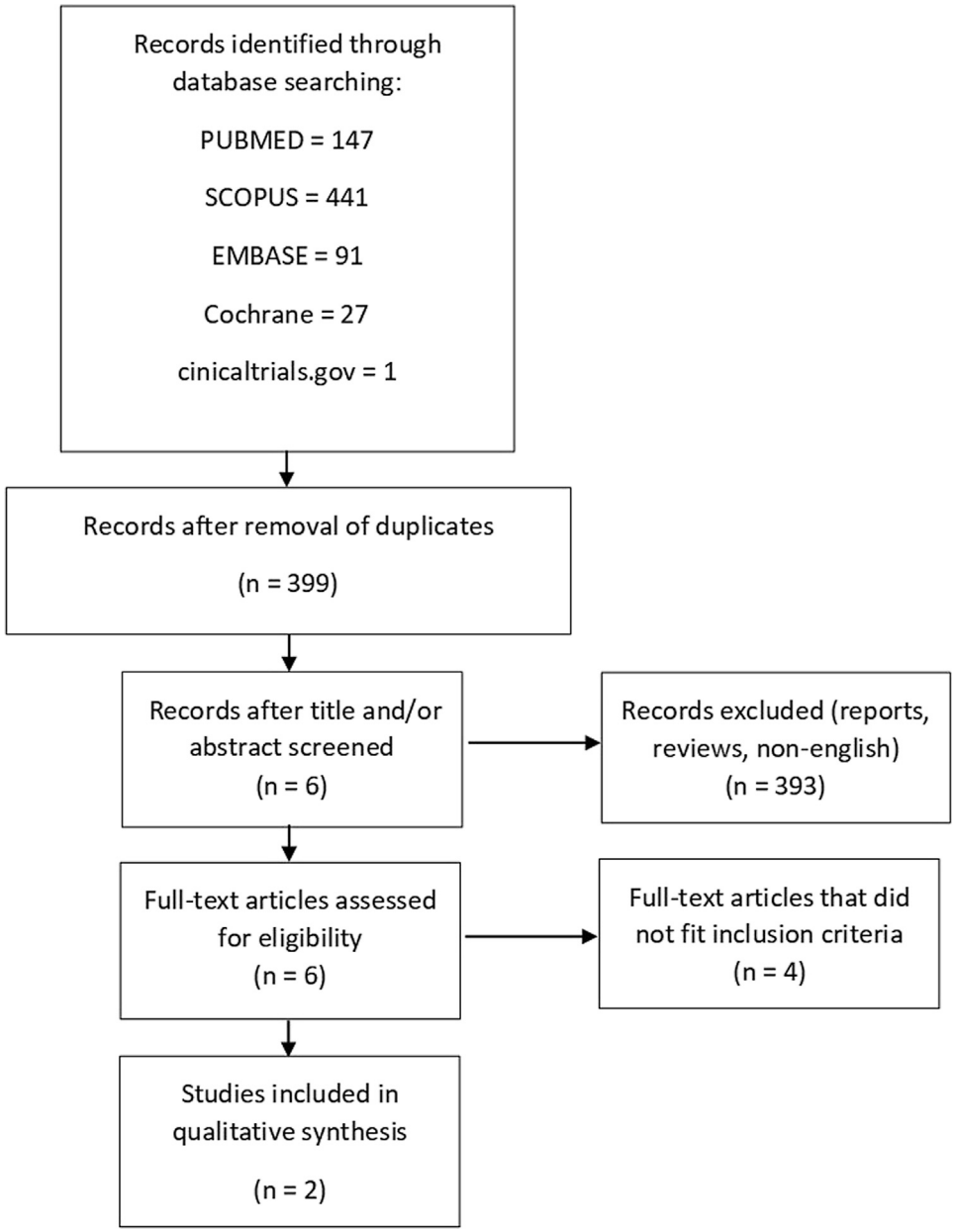

Fig 1. Flowchart of article selection process used for this review, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

topically in combination with laser.[1-3] Compared with intralesional injection, these alternate techniques deliver smaller amounts of bleomycin restricted to the wart lesion and should have fewer adverse effects. Thus, we aimed to evaluate head-to-head trials for the efficacy and safety of microneedling or the multiple puncture technique compared with intralesional bleomycin.

We conducted a systematic database search of PubMed, SCOPUS, Embase, and Cochrane Central Register of Controlled trials. Additionally, cinicaltrials.gov was searched for any completed trials. We included trials published in English, from the inception of the databases until April 2020, which compared the use of intralesional bleomycin with bleomycin delivery by microneedling or the multiple puncture technique in warts. We used broad search terms ("bleomycin" AND "wart") in all of the above-mentioned databases. Details of the PubMed search terms used are as follows: ("bleomycin"[Medical Subject Heading Terms] OR "bleomycin"[All Fields]) AND ("warts"[Medical Subject Heading Terms] OR "warts"[All Fields] OR "wart"[All Fields]). The details of article selection are presented in Fig 1. No trials

Table I. Study characteristics of the 2 head-to-head trials comparing intralesional (*IL*) and microneedling (*MN*) methods for bleomycin

Author, y	Study design	Total patients (MN, IL groups)	Intervention, comparator, dose	No. of warts treated per session	Interval	No. of sessions needed to achieve clearance	Treatment sessions	Micro results, (n)	IL results, (n)	Follow-up	Recurrence	Adverse effects in MN group	Adverse effects in IL group
Gamil,[4] 2019	Controlled clinical trial	54* (18, 18)	IL bleomycin, MN with topical bleomycin, 1 mg/mL	Not specified (1 to multiple)	2 wk	Not specified	Maximum of 4	Complete cure: 88.9% (16) Partial response: 11.1% (2)	Complete cure: 83.3% (15) Partial response: 16.7% (3)	6 mo	0 (both groups)	100% mild pain 11% hyperpigmentation	100% moderate pain 55.5% erythema 33.3% blister 16.6% hyperpigmentation 5.5% itching 5.5% infection
Al-Naggar,[1] 2018	Clinical trial	60 (30, 30)	IL bleomycin, MN with topical bleomycin, 1 mg/mL	Maximum 5 per session	2 wk	MN group 2.57 ± 0.86; IL group 3.3 ± 0.75 ($P < .001$)	Maximum of 4	Complete cure: 83.3% (25) Partial response: 16.7% (5)	Complete cure: 70% (21) Partial response: 30% (9)	3 mo	0 (both groups)	20% pain 53% erythema 16.7% edema	100% pain 47% erythema 20% edema

*Gamil et al included a third control group consisting of 18 patients who received saline.

comparing intralesional with the multiple puncture technique were found.

Two nonrandomized trials investigated bleomycin in a total of 96 patients with plantar warts.[4,5] Study characteristics are detailed in Table I.[1,4] Complete cure was significantly higher in the microneedling group compared with the intralesional group (85.5% vs 76.5%, respectively; $P < .001$). Pain was significantly more common with the intralesional method (50% vs 100%, $P < .001$). Gamil et al[4] reported hemorrhagic blisters in 33% of the intralesional group and in 0% of the microneedling group. Edema and erythema were not significantly different ($P = .06$). Nail dystrophy, Raynaud phenomenon, gangrene, or sclerodermatous changes were not observed in any patient. No systemic adverse effects were reported. There was no recurrence at the 6-month follow-up in any of the patients who achieved complete clearance by either method.

Our systematic search revealed 2 head-to-head trials comparing the microneedling method with the traditional intralesional injection for bleomycin delivery in plantar warts. We found that topical bleomycin with microneedling of the wart surface was associated with a higher cure rate than intralesional injection. A possible explanation may be perilesional extravasation with direct injection in contrast to the controlled drug delivery to the entire wart lesion ensured by the microneedling technique.[1] In addition, adverse effects, such as pain and hemorrhagic blisters, were more common with intralesional injection.

This review is limited by the paucity of trials conducted on the subject. There were also considerable differences in the microneedling process used in the trials.

In conclusion, microneedling as a modality of bleomycin delivery may be superior to intralesional injection in patient comfort, safety, and efficacy in plantar warts. There is a need for further research, especially to standardize the microneedling method and to compare the related multiple puncture technique with intralesional injection in head-to-head trials. Furthermore, adequately powered studies are needed to bring about practice change.

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REFERENCES

1. Al-Naggar MR, Al-Adl AS, Rabie AR, Abdelkhalk MR, Elsaie ML. Intralesional bleomycin injection vs microneedling-assisted topical bleomycin spraying in treatment of plantar warts. *J Cosmet Dermatol*. 2019;18(1):124-128.
2. Bik L, Sangers T, Greveling K, Prens E, Haedersdal M, van Doorn M. Efficacy and tolerability of intralesional bleomycin in dermatology: a systematic review [e-pub ahead of print]. *J Am Acad Dermatol*; 2020. https://doi.org/10.1016/j.jaad.2020.02.018. Accessed May 22, 2020.
3. Suh JH, Lee SK, Kim MS, Lee UH. Efficacy of bleomycin application on periungual warts after treatment with ablative carbon dioxide fractional laser: a pilot study. *J Dermatolog Treat*. 2020;31(4):410-414.
4. Gamil HD, Nasr MM, Khattab FM, Ibrahim AM. Combined therapy of plantar warts with topical bleomycin and microneedling: a comparative controlled study. *J Dermatolog Treat*. 2020;31(3):235-240.
5. Kwok CS, Gibbs S, Bennett C, Holland R, Abbott R. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev*. 2012;9:CD001781.

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Financial burden in US patients with melanoma from 1997 to 2015: Racial disparities, trends, and predictors of high expenditures

To the Editor: The incidence of melanoma has increased at a rate faster than that of most other cancers.[1] The cost of melanoma treatment has likewise significantly increased.[2] Although prior studies have examined racial/socioeconomic disparities in melanoma outcomes, disparities in health care costs and use have not yet been fully characterized. We used the nationally representative Medical Expenditure Panel Survey database to assess the individual and systemic financial burden in US patients with melanoma from 1997 to 2015 and identify trends, racial disparities, and predictors of high health care expenditures.

Of 221.5 million adult patients (weighted), 653,779 patients reported a diagnosis of melanoma and 13,151,022 reported a nonmelanoma cancer (Supplemental Methods; available via Mendeley at