

Symptomatic Dermographism: A Systematic Review of Treatment Options



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What is already known about this topic? Symptomatic dermographism is the most common type of chronic inducible urticaria. Little is known about the available treatment options and their efficacy. The recommended first-line therapy for symptomatic dermographism patients is second-generation H₁-antihistamines.

What does this article add to our knowledge? The available studies are heterogeneous, usually old, small, and often unrepeated, indicating a need for better studies. No studies exist on up dosing of second-generation H₁-antihistamines compared with the standard dosage in symptomatic dermographism.

How does this study impact current management guidelines? Second-generation H₁-antihistamines should be the first-line treatment of symptomatic dermographism. In uncontrolled cases, a combination of H₁-antihistamines and H₂-antihistamines or the up dosing of second-generation H₁-antihistamines may be considered. Omalizumab should be added for recalcitrant patients.

BACKGROUND: Symptomatic dermographism (SD), the most common form of chronic inducible urticaria, presents with transient wheals accompanied by itching in response to scratching. Little is known about available treatment options and their efficacy in SD.

OBJECTIVE: To systematically review the efficacy of treatment options for patients with SD.

METHODS: Using predefined search terms, we searched for relevant literature published until September 2019. The systematic review process was consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations.

RESULTS: The 23 studies identified included 15 randomized controlled trials; 22 and 17 assessed treatment responses in patients with SD by provocation/threshold testing and patient/physician clinical assessment, respectively. Thirteen different treatments were investigated in a total of 430 adult patients. The most frequently studied therapy, first-generation H₁-antihistamines, showed variable efficacy and significant side effects. In contrast, second-generation H₁-antihistamines (2ndAH₁), in all studies, were effective and well tolerated. Monotherapy with an H₂-antihistamine (AH₂) was not effective, whereas adding an AH₂ increased the efficacy of treatment with an H₁-antihistamine (AH₁). SD improved with omalizumab. All other treatments were only investigated in small, unrepeated, and/or uncontrolled studies. There are no studies on up dosing of 2ndAH₁.

CONCLUSIONS: The available SD studies are heterogeneous, mostly monocentric, old, small, and unrepeated, pointing to a high need for more and better studies. We suggest that 2ndAH₁ should be the first-line treatment. In uncontrolled cases, the combination of AH₁ and AH₂ may be tried. Even though there is no evidence of its efficacy over standard dosage, up dosing of 2ndAH₁ may be considered based on the extrapolation of evidence from chronic spontaneous urticaria; omalizumab should be added in recalcitrant patients. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3141-61)

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Abbreviations used

1stAH₁- First-generation H₁-antihistamines
 2ndAH₁- Second-generation H₁-antihistamines
 AH₁- H₁-Antihistamines
 AH₂- H₂-Antihistamines
 DLQI- Dermatology Life Quality Index
 NBUVB- Narrowband ultraviolet B
 PUVA- Psoralen and ultraviolet A
 QoL- Quality of life
 RCT- Randomized controlled trial
 SD- Symptomatic dermatographism
 VAS- Visual analog scale

Symptomatic dermatographism (SD) is the most common form of chronic inducible urticaria. SD is defined by itch and/or burning sensations and the development of linear wheals due to shear force acting on the skin.¹ Many patients describe chronic pruritus as “a skin crawling sensation” without a visible rash, which leads to scratching and linear wheals.² After exposure of the skin to friction (eg, after rubbing or scratching of the skin), a wheal-and-flare reaction usually appears within 1 to 5 minutes and lasts for 30 minutes.^{3,4} The pathogenesis of SD is still unclear, but it is held to involve the degranulation of dermal mast cells, their release of histamine and other proinflammatory mediators, and the subsequent increase in vascular permeability (extravasation) and stimulation of sensory skin nerves.⁵ Up to 5% of the general population are reported to have SD.⁴ SD affects mainly young adults.⁶

The reported mean disease duration ranges from 3.6 to 6.9 years^{5,7-14} (Table I). However, most studies assessed disease duration of SD in patients who still had the disease rather than patients who had undergone remission. The average disease duration is therefore longer, in some patients over the decades. Schoepke et al⁵ reported that the quality of life (QoL) was significantly impaired in 38 of 91 patients with SD (42%), and that in 7% of the 91 patients, a normal life was not possible.

A diagnosis of SD is made based on a patient's history and photo-documentation as well as provocation testing.¹ Provocation tests are usually performed on the volar forearm or upper back by stroking the skin with a smooth, blunt object, such as a wooden spatula or the blunt end of a pencil, or the writing end of a closed ball point pen. A positive result demonstrates a wheal-and-flare reaction within 10 minutes after provocation.^{1,3}

Standard commercial instruments have been developed to assess the trigger threshold of each patient. For example, the calibrated dermatographometer (HTZ Limited, New Addington, United Kingdom) is a pen-shaped device with a spring-loaded tip of 0.9 mm in width that applies a controlled pressure to the skin. It is used to diagnose SD and delayed pressure urticaria. The pressure range of the calibrated dermatographometer is 20 to 160 g/mm² (2.0×10^5 to 15.7×10^5 Pa). For diagnostic testing in patients suspected to have SD, the device is applied with a stroking motion in 3 parallel lines with pressures of 20 (2.0×10^5 Pa), 36 (3.6×10^5 Pa), and 60 (5.97×10^5 Pa) g/mm². The test response is read 10 minutes later and recorded as positive when a wheal and itch are present.¹ A pressure of ≤ 36 g/mm² (3.6×10^5 Pa) on the skin surface that is able to induce

TABLE I. The reported average duration of symptomatic dermatographism

Study	No. of patients	Mean duration before enrollment (±SD*)	Duration before enrollment (min to max)	Definition of remission
(A) Studies that reported the duration of SD [†] in patients who still had the disease at the time of enrollment				
Kaur et al 1981 ⁷	21	3.6 mo	2 mo to 19 y	—
Breathnach et al 1983 ¹³	50	5.1 (±1.2) y	3 mo to 47 y	—
Boyle et al 1989 ⁸	12	3.6 y	2 mo to 20 y	—
Lawlor et al 1989 ⁹	6	5.25 y	1.5 to 14 y	—
Logan et al 1989 ¹⁰	14	4.5 y	8 mo to 18 y	—
Borzova et al 2008 ¹¹	8	43.8 mo	1 to 7 y	—
Toda et al 2011 ¹²	6	6.9 y	0.5 to 15 y	—
(B) Studies that reported on the duration SD [†] in patients who had disease remission				
Silpa-archa et al 2011 ¹⁴	30	Median duration 60 mo	—	No urticarial wheal at least 6 mo after abandonment of a medication and negative dermatographometer test
Schoepke et al 2015 ⁵	150	6.25 y (±7.5 mo)	—	No urticarial wheal (no provocation test due to a self-administered questionnaire study)

*SD, standard deviation.

[†]SD, symptomatic dermatographism.

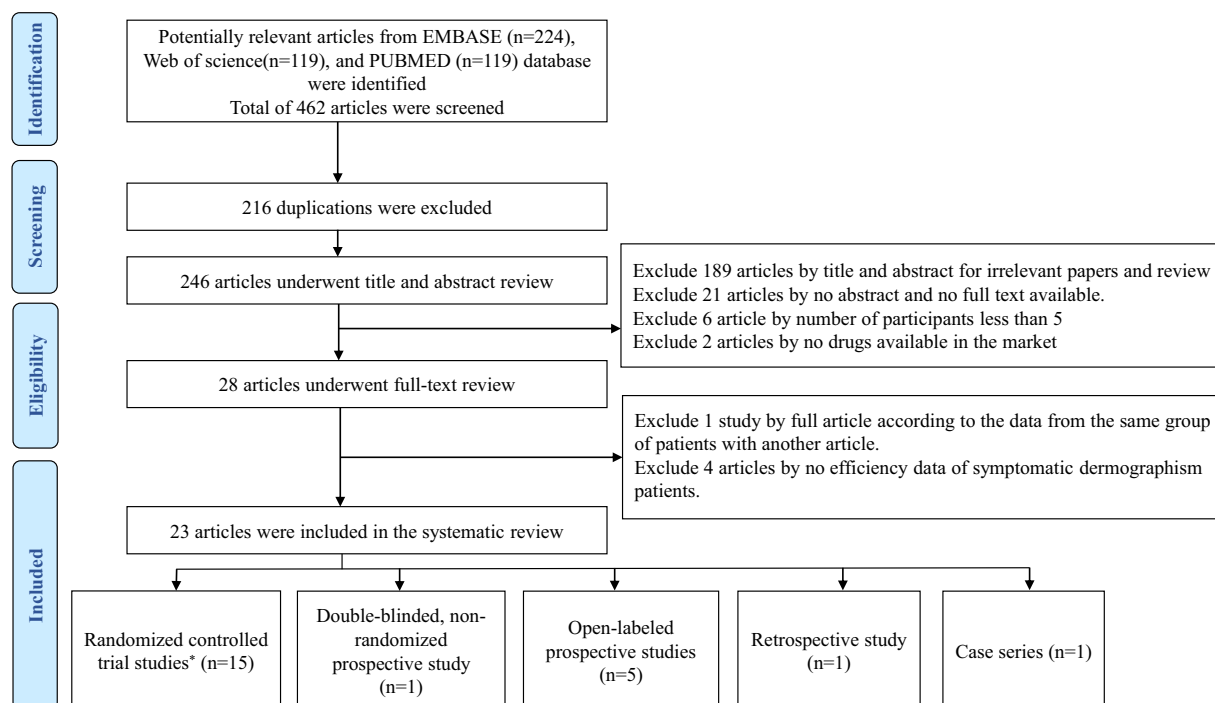


FIGURE 1. Flow diagram of the literature review in this systematic review. Twenty-three articles met the inclusion criteria and were included in our systemic review. Fifteen studies were randomized controlled trial studies,^{7-9,13,17,19-27,34} 1 study was a double-blinded, nonrandomized prospective study,²⁹ 5 studies were open-labeled prospective studies,^{10,11,28,30,31} 1 study was a retrospective study,³⁵ and 1 study was case series.¹² *Three included randomized controlled trial studies also contained the data of the withdrawn drugs (astemizole, 1 study²³; terfenadine, 2 studies^{8,26}).

a positive wheal-and-flare reaction is a reference measurement for the diagnosis of SD.

A Dermographism-Testing-and-Grading device (Dermograder, India) consists of a template and stroker that can adjust a trigger pressure by increasing the thickness of each stroker from 11 to 13 mm and from 15 to 17 mm. The least thickness makes the maximum press. There are 4 levels, ranging from grade I to grade IV.¹⁵

FricTest (Moxie, Berlin, Germany) is another standard qualitative instrument for diagnosing SD and for assessing trigger thresholds. The device is a plastic comb with 4 tips (3.0, 3.5, 4.0, and 4.5 mm in length) that applies 4 different grades of force when stroked once across the width of the volar forearm. A positive test result is defined as a pruritic wheal of width ≥ 3 mm within 10 minutes.^{1,16}

A dermatograph is a device used to scratch a patient's forearm to provoke SD symptoms (data about dermatographs are not available).¹⁷

Threshold testing with these instruments, that is, the determination of the lowest trigger strength that results in a wheal and itch response, is recommended to evaluate disease activity of patients before and after the initiation of treatment to assess their disease activity and therapeutic response.

Although patients with SD are advised to avoid relevant triggers of whealing (such as rubbing, scratching, and/or scrubbing), this is not always easy or possible.² Most patients require a medication that provides protection from friction-induced pruritus, whealing, and angioedema formation. The use of a second-generation H₁-antihistamines (2ndAH₁) at the

licensed dose is recommended by the current international guideline for chronic urticaria as the first-line treatment option for SD.^{1,18} When SD is insufficiently controlled by a standard-dosed 2ndAH₁, dose escalation to up to 4 times the standard dose is advised.^{1,18} The recommended treatment options for H₁-antihistamines (AH₁)-resistant patients with SD include omalizumab and ciclosporin.^{1,18} Other SD treatments used in daily clinical practice include first-generation H₁-antihistamines (1stAH₁), H₂-antihistamines (AH₂), serotonin antagonists, corticosteroids, nifedipine, phototherapy, and photochemotherapy.^{7-11,13,17,19-31} Currently, it is largely unclear how effective the available treatment options for patients with SD are. Our systematic literature review of randomized controlled trials (RCTs) and non-RCTs on SD aimed to provide this information to help guide the treatment of patients with SD and identify unmet needs in the management of this disease.

METHODS

Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations, a standard protocol for systematic review, were applied to this study.³² The literature search was conducted using 3 electronic databases (PubMed, Web of Science, and Embase) for papers published until September 2019, using the terms “symptomatic dermatographism,” “dermatographic urticaria,” “urticaria factitia,” and “urticaria facticia.”

TABLE II. Quality and risk-of-bias assessment of included articles: randomized controlled trials

Study, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessments (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Matthews et al 1973 ²⁰	Unclear	No bias	No bias	No bias	Present bias 12/45 patients (26.7%) lost to follow-up	Present bias*
Matthews et al 1979 ¹⁹	Unclear	No bias	No bias	No bias	Present bias 8/16 patients (50%) lost to follow-up	No bias
Kaur et al 1981 ⁷	Unclear	No bias	No bias	No bias	Present bias 7/21 patients (33.3%) lost to follow-up	No bias
Cook and Shuster 1983 ²¹	No bias	No bias	No bias	No bias	No bias	No bias
Breathnach et al 1983 ¹³	Unclear	No bias	No bias	No bias	Present bias 6/12 patients (50%) lost to follow-up	No bias
Mansfield et al 1983 ²²	Unclear	Unclear	Unclear	Unclear	No bias	No bias
Krause and Shuster 1985 ²³	Unclear	No bias	No bias	No bias	No bias	No bias
Lawlor et al 1988 ²⁴	Unclear	No bias	No bias	No bias	No bias	No bias
Lawlor et al 1989 ⁹	Unclear	No bias	No bias	No bias	Present bias 2/6 patients (33.3%) lost to follow-up	No bias
Boyle et al 1989 ⁸	Unclear	No bias	No bias	No bias	No bias	Present bias†
Sharpe and Shuster 1993 ²⁵ (study 1)	Unclear	No bias	No bias	No bias	No bias	No bias
Sharpe and Shuster 1993 ²⁶ (study 2)	Unclear	No bias	No bias	No bias	No bias	No bias
Daniel et al 1994 ²⁷	Unclear	No bias	No bias	No bias	No bias	Present bias†
Magerl et al 2009 ¹⁷	Unclear	No bias	No bias	No bias	No bias	No bias
Maurer et al 2017 ³⁴	Unclear	No bias	No bias	No bias	No bias	No bias

No bias, most information is from studies at low risk of bias; Unclear, plausible bias that raises some doubt about the results; Present bias, the proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

*No data of diazepam group were reported.

†Some patients' data were not reported.

TABLE III. Quality and risk-of-bias assessment of included articles: nonrandomized controlled trials

Study, year	Criteria						Additional criteria in the case on comparative study						
	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the study aim	Unbiased evaluation of endpoints	Follow-up period appropriate to the aim of the study	Loss to follow-up not exceeding 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total
Cap et al 1985 ²⁹	2	0	2	2	2	2	0	0	1	2	2	1	16
Toth-Kasa and Husz 1987 ²⁸	2	0	2	2	0	2	0	0	1	2	2	2	15
Logan et al 1989 ¹⁰	2	0	2	2	0	2	2	0	1	2	2	0	15
Kumar et al 2002 ³¹	2	0	2	2	0	1	2	0	—	—	—	—	9
Ayala and Nino 2003 ³⁰	2	0	2	2	2	2	2	0	—	—	—	—	12
Borzova et al 2008 ¹¹	2	1	2	2	0	2	2	0	—	—	—	—	11
Toda et al 2011 ¹²	2	0	2	1	0	2	2	0	—	—	—	—	9
Metz et al 2014 ³⁵	2	0	0	2	0	2	2	0	—	—	—	—	8

0, not reported; 1, reported but inadequate; 2, reported and adequate.

Eligibility criteria for systematic review

The eligibility criteria for reports to be included in our systematic review were as follows: (1) the study was an RCT, a retrospective cohort study, a double-blinded prospective study, or an open-label prospective study; (2) study participants were patients with SD; (3) at least 1 treatment that is available in the market was given to study participants; and (4) information on the treatment efficacy was provided. Non-RCTs that reported on less than 5 patients with SD were excluded to minimize selection bias. Studies on chronic urticaria without sufficient information on the patients with SD were also excluded. Three independent reviewers (KK, RK, and NJ) initially screened all titles and abstracts for eligibility. Potentially relevant articles were subsequently reviewed in full text to determine their final eligibility. This process was also independently conducted by the same reviewers. Disagreements were resolved by consensus-generating discussions between the reviewers.

Our search identified 462 potentially relevant articles (119 from PubMed, 119 from Web of Science, and 224 from Embase). After the exclusion of 216 duplicates, 246 studies were reviewed by title and abstract. Subsequently, 218 articles were excluded because they did not fulfill our inclusion criteria. The remaining 28 studies were evaluated in full length.

As 2 articles—one by Metz et al (poster abstract)³³ and the other by Maurer et al (full-text published article)³⁴—were actually the same study, only the full-text publication was included.³⁴ Four articles were excluded because they did not report on the efficacy of treatments. Finally, 23 studies fulfilled all of the eligibility criteria and were included in our systematic review (Figure 1). It should be noted that 3 included studies, in addition to reporting treatment effects, also present information on the withdrawal of drugs (astemizole, 1 study²³; terfenadine, 2 studies^{8,26}), which we do not discuss in the present review.

Data extraction

The following data were extracted from each study: (1) the first author's name and the publication year; (2) the study design; (3) the numbers of treated patients with SD and (if any) control patients; (4) the name and route of administration of medication(s); (5) the dose and duration of treatment; (6) the outcomes; and (7) the treatment side effects. The data extraction process was independently performed by the same 3 investigators for all articles.

Assessment of bias risks and quality of evidence

(Tables II-IV)The Cochrane Collaboration's tool was applied to assess the risk of bias of the included RCTs,³⁶ and the Methodological Index for Non-Randomized Studies was used to assess the risk of bias of the non-RCTs.³⁷ In addition, the quality of each outcome was categorized as high, moderate, low, and very low, using the Grading of Recommendations Assessment, Development and Evaluation system.³⁸

RESULTS

The 23 included studies were performed on 430 adult patients with SD. Fifteen of the studies were RCTs,^{7-9,13,17,19-27,34} whereas 8 were non-RCTs^{10-12,28-31,35} (1 double-blinded, non-randomized prospective study²⁹; 5 open-label prospective studies^{10,11,28,30,31}; 1 retrospective study³⁵; and 1 case series¹²) (Tables V and VI). The number of patients per study ranged from 6 to 61. The studies were performed ≥ 40 years ago (n = 2)^{19,20}; 30 to 39 years ago (n = 11)^{7-10,13,21-24,28,29}; 20 to 29 years ago (n = 3)²⁵⁻²⁷; 10 to 19 years ago (n = 4)^{11,17,30,31}; and

TABLE IV. Summary of medications used in all randomized controlled trials (RCT) and non-RCT studies, with the level of the quality of the evidence according to the GRADE system

Medication	Outcome measurement	No. of studies	Efficacy*	Results	Quality of evidence†						Reference, year
					LIM	INC	IND	IMP‡	PB§	Quality	
Antihistamines											
First-generation antihistamines alone	Provocation with dermographometer	6	+	Two studies showed a significant reduction in wheal size using chlorpheniramine compared with cimetidine alone ^{7,19} and placebo ⁷	S	S	NS	N/A	N/A	Low	Matthews et al 1973 ²⁰ (RCT) Matthews et al 1979 ¹⁹ (RCT) Kaur et al 1981 ⁷ (RCT) Breathnach et al 1983 ¹³ (RCT) Krause and Shuster 1985 ²³ (RCT) Daniel et al 1994 ²⁷ (RCT)
				One study showed a significant reduction in wheal size using hydroxyzine compared with chlorpheniramine ²⁰							
				One study showed a reduction in wheal and flare size using trimeprazine and hydroxyzine compared with other antihistamines ¹³							
				One study showed a reduction in wheal size using chlorpheniramine compared with placebo ²³							
				One study showed that ketotifen was effective for reducing wheal and wheal response clearing compared with placebo ²⁷							
	2	—	One study showed no significant reduction in wheal size using chlorpheniramine ²¹	S	NS	NS	N/A	N/A	Moderate	Cook and Shuster 1983 ²¹ (RCT)	
			One study showed no significant inhibition of wheal response using chlorpheniramine ²²							Mansfield et al 1983 ²² (RCT)	
	Subjective assessment	4	+	One study showed relief of itch in hydroxyzine group and chlorpheniramine group ²⁰	S	S	NS	N/A	N/A	Low	Matthews et al 1973 ²⁰ (RCT) Breathnach et al 1983 ¹³ (RCT) Cap et al 1985 ²⁹ (non-RCT)
One study showed good efficacy evaluation by patients using hydroxyzine and cyproheptadine compared with other antihistamines ¹³											
One study showed that ketotifen improved itch and wheal formation by patients' self-assessment compared with placebo ²⁹											
	2	—	One study showed that chlorpheniramine alone had no clinical improvement in patients with SD ¹⁹	S	S	NS	N/A	N/A	Low	Matthews et al 1979 ¹⁹ (RCT) Krause and Shuster 1985 ²³ (RCT)	
			One study showed relief of itch by patient evaluation using chlorpheniramine ²³								
Second-generation H ₁ -antihistamines alone	Provocation with dermographometer or dermograph	5	+	Two studies showed that cetirizine had significantly increased wheal threshold compared with placebo ^{25,26}	S	S	NS	N/A	N/A	Low	Boyle et al 1989 ⁸ (RCT) Sharpe and Shuster 1993 ²⁵ study 1 (RCT) Sharpe and Shuster 1993 ²⁶ study 2 (RCT) Ayala and Nino 2003 ³⁰ (non-RCT) Magerl et al 2009 ¹⁷ (RCT)
				One study showed that acrivastine had a significant reduction in wheal and flare size compared with placebo and baseline ⁸							
				One study showed that desloratadine had improvement in SD lesions ³⁰							
				One study showed that ebastine had a significant reduction in wheal size compared with placebo ¹⁷							
	Subjective assessment	5	+	Three studies showed a significant reduction in wheal size and itch assessed by patients using acrivastine ⁸ and cetirizine ^{25,26}	S	S	NS	N/A	N/A	Low	Boyle et al 1989 ⁸ (RCT) Sharpe and Shuster 1993 ²⁵ study1 (RCT) Sharpe and Shuster 1993 ²⁶ study 2 (RCT) Kumar et al 2002 ³¹ (non-RCT) Ayala and Nino 2003 ³⁰ (non-RCT)
One study showed that cetirizine had complete protection from the development of wheal ³¹											
One study showed improvement in pruritus using desloratadine ³⁰											

H ₂ -antihistamines alone	Provocation with dermographometer	4	—	Two studies showed no significant reduction in wheal and flare size using cimetidine compared with the combination of chlorpheniramine and cimetidine and chlorpheniramine alone ^{7,19} One study showed cimetidine alone had no significant reduction in wheal size ²¹ One study showed cimetidine alone had no significance in inhibition of wheal response ²²	S	NS	NS	N/A	N/A	Moderate	Matthews et al 1979 ¹⁹ (RCT) Kaur et al 1981 ⁷ (RCT) Cook and Shuster 1983 ²¹ (RCT) Mansfield et al 1983 ²² (RCT)
	Subjective assessment	1	—	One study showed cimetidine alone worsened overall clinical response by patients ¹⁹	S	N/A	NS	N/A	N/A	Moderate	Matthews et al 1979 ¹⁹ (RCT)
H ₁ and H ₂ antihistamines	Provocation with dermographometer	6	+	Two studies showed a significant reduction in wheal and flare size using the combination of chlorpheniramine and cimetidine compared with chlorpheniramine alone and cimetidine alone ¹⁹ and placebo ⁷ Two studies showed a significant inhibition of wheal response using the combination of chlorpheniramine and cimetidine ²² and the combination of cetirizine and ranitidine ²⁶ One study showed a significant reduction in wheal size using the combination of chlorpheniramine and cimetidine compared with cimetidine alone and chlorpheniramine alone ²¹ One study showed a significant reduction in wheal size using the combination of hydroxyzine and cimetidine compared with other antihistamines ¹³	S	NS	NS	N/A	N/A	Moderate	Matthews et al 1979 ¹⁹ (RCT) Kaur et al 1981 ⁷ (RCT) Cook and Shuster 1983 ²¹ (RCT) Breathnach, et al. 1983 ¹³ (RCT) Mansfield et al 1983 ²² (RCT) Sharpe and Shuster 1993 ²⁶ study 2 (RCT)
	Subjective assessment	2	+	One study showed significant improvement in overall clinical response by patients using cimetidine and chlorpheniramine compared with each drug alone ¹⁹ One study showed that the combination of hydroxyzine and cimetidine was the first ranked order of efficacy evaluated by patients ¹³	NS	NS	NS	N/A	N/A	High	Matthews et al 1979 ¹⁹ (RCT) Breathnach et al 1983 ¹³ (RCT)
		1	—	One study showed no significant improvement in disease severity assessed by patients using the combination of cetirizine and ranitidine ²⁶	S	N/A	NS	N/A	N/A	Moderate	Sharpe and Shuster 1993 ²⁶ study 2 (RCT)
Antihistamines + oral corticosteroids	Provocation with dermograder	1	+	One study showed improvement in the decrease of the dermograde using the combination of cetirizine and oral betamethasone ³¹	S	N/A	NS	N/A	N/A	Very low	Kumar et al 2002 ³¹ (non-RCT)
	Subjective assessment	1	+	One study showed improvement in complete protection from the development of wheals using the combination of cetirizine and oral betamethasone ³¹	S	N/A	NS	N/A	N/A	Very low	Kumar et al 2002 ³¹ (non-RCT)
Antihistamines + cyclophosphamide	Provocation with dermograder	1	—	One study showed no improvement in the decrease of the dermograde using the combination of cetirizine and cyclophosphamide ³¹	S	N/A	NS	N/A	N/A	Very low	Kumar et al 2002 ³¹ (non-RCT)
	Subjective assessment	1	+	One study showed improvement in complete protection from the development of wheals using the combination of cetirizine and cyclophosphamide ³¹	S	N/A	NS	N/A	N/A	Very low	Kumar et al 2002 ³¹ (non-RCT)

(continued)

TABLE IV. (Continued)

Medication	Outcome measurement	No. of studies	Efficacy*	Results	Quality of evidence†					Quality	Reference, year
					LIM	INC	IND	IMP‡	PB§		
Antihistamines + serotonin antagonist	Provocation with 15-cm-long blunt end of a pencil	1	+	One study showed a significant reduction in wheal and flare size using the combination of cinnarizine and pizotifen ²⁸	S	N/A	NS	N/A	N/A	Very low	Toth-Kasa and Husz 1987 ²⁸ (non-RCT)
	Subjective assessment	1	+	One study showed improvement in itch reduction using the combination of cinnarizine and pizotifen ²⁸	S	N/A	NS	N/A	N/A	Very low	Toth-Kasa and Husz 1987 ²⁸ (non-RCT)
Omalizumab	Provocation with FricTest	2	+	Two studies showed that omalizumab could improve a reduction in provocation threshold ^{34,35}	NS	N/A	NS	N/A	N/A	High	Metz et al 2014 ³⁵ (non-RCT) Maurer et al 2017 ³⁴ (RCT)
	Subjective assessment	2	+	One study showed that omalizumab had improvement in symptoms as assessed by patient global assessment ³⁵ One study showed that omalizumab had improvement in symptoms as assessed by the DLQI ³⁴	NS	NS	NS	N/A	N/A	High	Metz et al 2014 ³⁵ (non-RCT) Maurer et al 2017 ³⁴ (RCT)
Ciclosporin	Provocation with dermatographometer	1	+	One study showed a decrease in flare size using ciclosporin ¹²	S	N/A	NS	N/A	N/A	Very low	Toda et al 2011 ¹² (non-RCT)
	Subjective assessment	1	+	One study showed improvement in itch using ciclosporin ¹²	S	N/A	NS	N/A	N/A	Very low	Toda et al 2011 ¹² (non-RCT)
Other drugs											
Nifedipine	Provocation with dermatographometer	1	–	One study showed that nifedipine had no significant reduction in wheal size ²⁴	NS	N/A	NS	N/A	N/A	High	Lawlor et al 1988 ²⁴ (RCT)
	Subjective assessment	1	–	One study showed that nifedipine had no significant improvement of itch ²⁴	NS	N/A	NS	N/A	N/A	High	Lawlor et al 1988 ²⁴ (RCT)
Topical corticosteroids	Provocation with dermatographometer	1	+	One study showed significant reduction in wheal width using topical clobetasol ⁹	S	N/A	NS	N/A	N/A	Moderate	Lawlor et al 1989 ⁹ (RCT)
	Subjective assessment	1	+	One study showed improvement of itch using topical clobetasol ⁹	S	N/A	NS	N/A	N/A	Moderate	Lawlor et al 1989 ⁹ (RCT)
Psoralen and ultraviolet A	Provocation with dermatographometer	1	–	One study showed no significant reduction in wheal size using psoralen and ultraviolet A ¹⁰	S	N/A	NS	N/A	N/A	Very low	Logan et al 1989 ¹⁰ (non-RCT)
	Subjective assessment	1	–	One study showed no significant reduction in severity of itch using psoralen and ultraviolet A ¹⁰	S	N/A	NS	N/A	N/A	Very low	Logan et al 1989 ¹⁰ (non-RCT)
Narrowband ultraviolet B	Provocation with dermatographometer	1	+	One study showed that narrowband ultraviolet B led to significant reduction in wheal size compared with baseline ¹¹	S	N/A	NS	N/A	N/A	Very low	Borzova et al 2008 ¹¹ (non-RCT)
	Subjective assessment	1	+	One study showed that narrowband ultraviolet B had significant reduction in wheal size and pruritus by patient' self-assessment compared with baseline ¹¹	S	N/A	NS	N/A	N/A	Very low	Borzova et al 2008 ¹¹ (non-RCT)

DLQI, Dermatology Life Quality Index; N/A, data not available in this study; NS, not serious; RCTs, randomized control trial studies; S, serious; SD, symptomatic dermatographism.

*Efficacy of the study: (+) = study supports efficacy of treatment; (–) = study does not support efficacy of treatment.

†According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, for classification of evidence: the quality of evidence at 1 of 4 levels: high, moderate, low, and very low, based on 5 downgrade factors: LIM (limitations), (INC) inconsistency, (IND) indirectness, (IMP) imprecision, and (PB) publication bias.

‡The imprecision is to be assessed by the effect size and 95% confidence interval. This criterion was not evaluated in our review.

§Assessment of publication bias using the funnel plot. This criterion was not evaluated in our review. However, as our study is a systematic review without meta-analysis, the imprecision and publication bias cannot be evaluated.

TABLE V. Characteristics of included randomized controlled trials studies in patients with symptomatic dermographism

Study, year	Treatment methods	Measurement of response/devices/ parameters	Results			
			Reduction of wheals and flare	Subjective assessments	Side effects	Conclusion
Matthews et al 1973 ²⁰ (Crossover)	N = 45 (dropout 12) (1) Hydroxyzine pamoate 75 mg/d (2) Chlorpheniramine maleate 12 mg/d (3) Diazepam 6 mg/d Duration: 2 wk for each treatment, no washout period	• Dermographometer - Wheal size reduction when applying at pressures of 3650 and 7400 g/cm² • Symptomatic relief of itch	• The reduction of wheal size with hydroxyzine was significantly greater than with chlorpheniramine at pressures of 3650 and 7400 g/cm² on the arm and a pressure of 7400 g/cm² on the back • The efficacy of diazepam in reduction of wheal size was not mentioned	• 29/33 patients: relief of itch in hydroxyzine group • 16/33 patients: some relief from itch in chlorpheniramine group • The comparisons among hydroxyzine, chlorpheniramine, and diazepam were not mention	• Hydroxyzine 5/33 patients: drowsiness • Chlorpheniramine • 2/33 patients: complained of excessive tiredness	• Hydroxyzine led to a greater reduction of wheal size than chlorpheniramine did
Matthews et al 1979 ¹⁹ (Crossover)	N = 16 (1) Chlorpheniramine 16 mg/d and cimetidine 1600 mg/d (dropout 6) (2) Chlorpheniramine 16 mg/d and placebo (dropout 6) (3) Cimetidine 1600 mg/d and placebo (dropout 8) Duration: 2 wk for each protocol, no washout period	• Dermographometer - Wheal and flare size diameter (at pressures of 4900 and 7350 g/cm²) • Overall clinical response by patients graded as followed: much improved, slightly improved, same, slightly worse, much worse	• The combination of chlorpheniramine and cimetidine had a greater wheal reduction than chlorpheniramine alone only at a pressure of 7350 g/cm² (P < .001) • The combination of chlorpheniramine and cimetidine and chlorpheniramine alone were significantly more effective in inhibiting flare than cimetidine alone (P < .02)	• Chlorpheniramine and cimetidine produced a significant improvement in patients' overall clinical response (P < .05) • Chlorpheniramine alone did not improve patients' overall clinical response • Cimetidine alone significantly worsened overall clinical response (P < .025)	• Chlorpheniramine 16 mg/d and cimetidine 1600 mg/d • 1/10 patient complained of moderate drowsiness • Chlorpheniramine alone • 1/10 patient complained of aching legs • Cimetidine alone • 1/8 patient complained of itchy eyes • No clinically significant changes in laboratory tests on blood and urine were reported during the study of all drugs	• The combination of chlorpheniramine and cimetidine had a great reduction in the wheal and flare response
Kaur et al 1981 ⁷ (Crossover)	N = 21 (dropout 7) (1) Chlorpheniramine 1600 mg/d and cimetidine 16 mg/d	• Dermographometer - Wheal size 0 = absent 1 = mild (2 mm) 2 = moderate (2-4 mm) 3 = severe (4 mm)	• The combination of chlorpheniramine and cimetidine was significantly effective in reducing wheal (P < .01) and flare sizes (P < .01) and duration of wheal (P < .01), compared with placebo	N/A	• No significant side effects were reported • Normal routine laboratory	• The combination of chlorpheniramine and cimetidine was the only treatment that significantly reduced wheal size, flare

(continued)

TABLE V. (Continued)

Study, year	Treatment methods	Measurement of response/devices/ parameters	Results			
			Reduction of wheals and flare	Subjective assessments	Side effects	Conclusion
	(2) Chlorpheniramine 16 mg/d and placebo (3) Cimetidine 1600 mg/d and placebo (4) Placebo Duration: 2 d for each protocol, with washout period for 5 d and continued the best reduction regimen for 3 mo	- Flare size - Duration of wheal 0 = zero 1 = short (30 min) 2 = moderate (30-60 min) 3 = severe (60 min)	Chlorpheniramine alone was more effective than cimetidine alone or placebo		tests	size, and duration of wheal
Cook and Shuster 1983 ²¹ (Crossover)	N = 20 (1) Chlorpheniramine 4 mg and cimetidine 400 mg (2) Chlorpheniramine 4 mg and placebo (3) Cimetidine 400 mg and placebo Duration: took medicine once, 2 d for washout period	- Dermographometer -Wheal diameter using dose-response curves at pressures 24.5 g/mm² 48.6 g/mm² 60.9 g/mm² 74.6 g/mm²	- The dose-response curves showed that the combination of chlorpheniramine and cimetidine reduced the wheal response significantly, compared with untreated patients (P < .01) and with patients taking either chlorpheniramine or cimetidine alone (P < .05) - Either chlorpheniramine or cimetidine alone did not reduce the wheal response significantly	N/A	N/A	The combination of chlorpheniramine and cimetidine was more effective than either drug alone
Breathnach et al 1983 ¹³ (Crossover)	N = 12 (dropout 6) (1) Hydroxyzine 40 mg/d and cimetidine 1600 mg/d (2) Chlorpheniramine 16 mg/d (3) Mepyramine 150 mg/d (4) Promethazine 50 mg/d (5) Ketotifen 2 mg/d (6) Trimeprazine 30 mg/d (7) Cyproheptadine 16 mg/d (8) Hydroxyzine 40 mg/d Duration: 5 d for each protocol, 2 d for washout period	- Dermographometer - Wheal diameter at pressures 3.5 × 105 Pa 6.7 × 105 Pa 9.4 × 105 Pa - Efficacy evaluation by patients (a scale of 0-4)	- At the highest pressure (9.4 × 105 Pa), the combination of hydroxyzine and cimetidine was significantly superior (P < .05) to all other treatments in reducing wheals - The combination of hydroxyzine and cimetidine was the first ranked order of average percent reduction in wheal width, followed by trimeprazine (second) and hydroxyzine (third)	The combination of hydroxyzine and cimetidine was the first ranked order of efficacy, followed by hydroxyzine (second) and then cyproheptadine (third)	- The main side effect in all treatments was drowsiness - Drowsiness was severe with trimeprazine and 4/12 patients discontinued trimeprazine before the ending 1/12 patient complained of nightmare while taking trimeprazine	The combination of hydroxyzine and cimetidine was significantly superior to all other treatments
Mansfield et al 1983 ²² (Crossover)	N = 11 chronic idiopathic urticaria associated with dermatographia (1) Chlorpheniramine 32 mg/d and cimetidine 1200 mg/d (2) Chlorpheniramine 32 mg/d	- Dermographometer - Degree of pressure to cause 3 mm or greater wheals	- The combination of chlorpheniramine and cimetidine was the greatest inhibition of whealing response and the inhibition was significant when compared with baseline (P = .01) and chlorpheniramine alone (P = .05) - Chlorpheniramine alone did not result in a significant inhibition of wheal response. - Cimetidine alone did not result in a significant inhibition of wheal response	N/A	N/A	The combination of chlorpheniramine and cimetidine reduced wheal response significantly superior to other treatments

(3) Cimetidine

1200 mg/Duration: 3
d for each protocol, 4
d washout period

Krause and Shuster
1985²³

N = 8

(1) Chlorpheniramine
12 mg/d (N = 8,
dropout 1) for 4 wk
and then placebo for
4 wk

Duration: 8 wk

- Dermographometer
 - Wheal diameter using a force-response curve
 - Wheal threshold
- Severity of itch (by 10 cm analog scale)
- Number of attacks

- The force-response curve demonstrated right shifted in chlorpheniramine group compared with pretreatment in week 2
- The maximum decrease in dermographic potency was 37% for chlorpheniramine (at week 2)
- After 4 wk, chlorpheniramine treatment wheal threshold increased from the treatment but was not statistically significant

- The mean daily itch at 4 wk of chlorpheniramine was less than the 4 subsequent weeks of placebo: neither differed significantly from the pre-treatment level

- Drowsiness was not a problem in chlorpheniramine
- Dry mouths were reported by 2/7 on chlorpheniramine
- There was a slight decrease in body weight in patients who received chlorpheniramine; these were not significant

- Chlorpheniramine improved both subjective and objective outcomes

Lawlor et al 1988²⁴
(Crossover)

Trial 1

N = 13 (dropout 2)

(1) Nifedipine 15 mg/d

(2) Placebo

Duration 2 wk for each
protocol, no washout
time

- Dermographometer
 - Whealing response at pressures
 - 2×105 Pa
 - 5.87×105 Pa
 - 9.75×105 Pa
 - 14.12×105 Pa
- Subjective assessment of itch (by VAS)

- There was no different reduction in whealing response in nifedipine compared with placebo (except at the highest pressure in study 1)

- Subjective assessment of itch
 - 5/11 patients had an improvement with nifedipine compared with placebo
 - 4/11 patients felt little different
 - 2/11 patient had no response to either treatment
- There was no statistical significance in the improvement

- Side effects of postural hypotension in 1 patient who dropped out of this study

- There was no consistent effect of nifedipine on SD
- Nifedipine could not be recommended as first-time treatment in SD

(Crossover)

Trial 2

N = 8 (dropout 1)

(1) Nifedipine 30 mg/d

(2) Placebo

Duration 2 wk for each
protocol, 1-wk washout
time

- Dermographometer
 - Wheal diameter at pressures
 - 1.6×105 Pa
 - 3.4×105 Pa
 - 5.8×105 Pa
 - 10×105 Pa
- A daily overall assessment on a VAS
- Subjective symptom assessment of the severity and frequency of whealing and itch (a scale of 0-4)

- VAS showed overall clinical improvement with nifedipine in 1/7 patient, no change in 3/7 patients and worsening compared with placebo in 3/7 patients
- There was no change in wheals and pruritus with

- Dizziness and headache were reported in 3/7 patients who had nifedipine
- One patient who dropped out of this study complained of intolerable headaches, postural dizziness, and edema

(continued)

TABLE V. (Continued)

Study, year	Treatment methods	Measurement of response/devices/ parameters	Results															
			Reduction of wheals and flare	Subjective assessments	Side effects	Conclusion												
				nifedipine according to subjective symptom assessment														
Lawlor et al 1989 ⁹	N = 6 (dropout 2) (1) Clobetasol propionate 0.05% ointment (2) Ointment base Apply one treatment on 10 cm2 the right anterior thigh and the other to the left anterior thigh Duration: 6 wk	• Dermographometer - Wheal width and itch at pressures 2.0 × 105 Pa 5.87 × 105 Pa 9.75 × 105 Pa 14.12 × 105 Pa • Skin biopsy - Mast cell count - Histamine level • Flare area after intradermal injection of compound 48/80 and histamine (2/6 patients)	• At each pressure, the changes in wheal width after clobetasol treatment were significantly more than those after ointment base (P < .05) Other objective assessment - Mast cell count and histamine level reduced by application of the steroid, compared with ointment base (P < .02 and, P < .05, respectively) - After intradermal injections of compound 48/80, 2/2 showed a decrease in flare areas in clobetasol pretreated skin, compared with ointment base treated sites. Flare areas after histamine injection in 2/2 patients were equivalent in all sites.	Itch occurred in the wheal, stroked areas but was not a prominent symptom	N/A	• Long-term application of a potent topical corticosteroid in patients with SD decreased wheal in response to stroking, mast cell numbers, skin histamine levels, and flare areas after intradermal injection of compound 48/80												
Boyle et al 1989 ⁸ (Crossover)	N = 12 (1) Acrivastine 8 mg 3 times a day (days 1-4) 8 mg/d (day 5) (2) Placebo Duration: 5 d for each protocol, 2 d washout period	• Dermographometer- Wheal and flare area (at 8, 12 oz) • Patients' self-assessment - Percent of patients with clinical improvement - Symptom score (itch and whealing; score 0-4) - Degree of improvement (score 0-3) - VAS (0-100 mm) • Physician's assessment of symptoms improvement	<table><thead><tr><th></th><th>Wheal area (mm²)</th><th>Flare area (mm²)</th></tr></thead><tbody><tr><td>Baseline</td><td>223.5</td><td>1704</td></tr><tr><td>Acrivastine</td><td>118.6*</td><td>774*</td></tr><tr><td>Placebo</td><td>208.3</td><td>1879</td></tr></tbody></table>		Wheal area (mm ²)	Flare area (mm ²)	Baseline	223.5	1704	Acrivastine	118.6*	774*	Placebo	208.3	1879	• All patients from acrivastine groups reported clinical improved (P < .01; compared with placebo) • Mean wheals scores - Acrivastine: 1.71 (P < .05 vs placebo) • Mean itch scores - Acrivastine: 1.60 (P < .05 vs placebo) • Mean degree of improvement scores - Acrivastine: 1.58 (P < .01 vs placebo) • Mean VAS - Acrivastine: 16.8 (P < .01 vs placebo) • Physician's assessment of symptoms improvement reported wheals and itch were reduced in 92%	N/A	• Acrivastine was well tolerated and significantly effective over placebo
	Wheal area (mm ²)	Flare area (mm ²)																
Baseline	223.5	1704																
Acrivastine	118.6*	774*																
Placebo	208.3	1879																

Sharpe and Shuster 1993 ²⁵ (study 1) (Crossover)	N = 21 (dropout 2) (1) Cetirizine 10 mg/d (2) Placebo Duration: 7 d for each protocol, with washout period for 3 d	• Dermographometer - Wheal response at pressures 17.5-95.5 g/mm² - Frictional force/wheal response curve - Wheal threshold • Patient's symptom diaries: description of wheal and itch using 100 mm VAS • A number of patients with night disturbance • Severity assessment by patients (score 1-5) and doctor (score 1-3)	• Frictional force/wheal response curve showed right and downward shift of the curve in cetirizine group • Wheal threshold in cetirizine group was significantly increased (P = .00001)	of patients from acrivastine (P < .05 vs placebo) • Mean patients' symptom score - Wheals: cetirizine vs placebo = 1 6.8 vs 34.3 (P = .02) - Itch: cetirizine vs placebo = 19.4 vs 43.2 (P = .001) • A number of patients with night disturbance: cetirizine vs placebo = 4/19 vs 13/19 (P = .03) • Mean severity scores assessed by patients: cetirizine vs placebo = 1.7 vs 3.9 • Mean severity scores assessed by physician: cetirizine vs placebo = 1.2 vs 2.1	N/A	• Cetirizine 10 mg/d was effective in the treatment of SD
Sharpe and Shuster 1993 ²⁶ (study 2) (Crossover)	N = 21 (dropout 2) (1) Cetirizine 10 mg/d and ranitidine 300 mg/d (2) Cetirizine 10 mg/d and placebo (3) Placebo Duration: 7 d for each protocol, with washout period for 3 d and placebo for 7 d between 2 active treatments	• Dermographometer - Wheal response at pressures 17.5-95.5 g/mm² using frictional force/wheal response curve and wheal threshold • Patient's symptom diaries: description of wheal and itch using 100 mm VAS • A number of patients with night disturbance • Patients' severity assessment (scores 1-5) and doctor (scores 1-3)	• Wheal response: - Frictional force/wheal response curve showed a large reduction in cetirizine group and a little smaller reduction in cetirizine and ranitidine - Wheal threshold in both cetirizine and combination of cetirizine and ranitidine groups was significantly increased (P = .00001)	• There was a significant reduction in wheals and itch, a number of patients with night disturbance and disease severity in cetirizine group • There was no difference in disease severity, assessed by patients or physician for cetirizine vs the combination of cetirizine and	N/A	• Adding H2 antihistamines to H1 antihistamines gave a small significant reduction in wheal response, but no symptomatic benefit

(continued)

TABLE V. (Continued)

Study, year	Treatment methods	Measurement of response/devices/ parameters	Results			Subjective assessments	Side effects	Conclusion								
			Reduction of wheals and flare													
Daniel et al 1994 ²⁷ (Crossover)	N = 24 (1) Ketotifen 2 mg/d (N = 24; 11 patients at first then 13 patients who failed to response to placebo switched to ketotifen) (2) Placebo (N = 11) Duration: 8 wk for each protocol (if there was no improvement in 2 wk, the patient would receive the other drug), without washout period	• Dermographometer - Wheal size reduction - Wheal response clearing	<table><thead><tr><th></th><th>Wheal size</th><th>Wheal response clearing (N/total)</th></tr></thead><tbody><tr><td>Ketotifen</td><td>Decreased by 0.79 mm</td><td>7/19</td></tr><tr><td>Placebo</td><td>Increased by 0.08 mm</td><td>N/A</td></tr></tbody></table>		Wheal size	Wheal response clearing (N/total)	Ketotifen	Decreased by 0.79 mm	7/19	Placebo	Increased by 0.08 mm	N/A	N/A	ranitidine, and no clear final patient preference	• Mild sedation and increased appetite were reported in 4/24 patients during the initial days of treatment with ketotifen	• Treatment with ketotifen showed symptomatic improvement • Recurrence within a few days after stopping ketotifen might occur
	Wheal size	Wheal response clearing (N/total)														
Ketotifen	Decreased by 0.79 mm	7/19														
Placebo	Increased by 0.08 mm	N/A														
Magerl et al 2009 ¹⁷ (Crossover)	N = 7 (1) Ebastine 20 mg single dose (2) Placebo single dose	• Dermograph - Response after scratching with a dermatograph	• There was a significant wheal reduction in ebastine group (P < .05)	N/A		• Cognitive performance and mood between ebastine and placebo were not different	• Ebastine was safe and effective in prevention of SD symptoms									
Maurer et al 2017 ³⁴	N = 61 (dropout 6) (1) Omalizumab 150 mg (N = 18) (2) Omalizumab 300 mg (N = 19) (3) Placebo (N = 18) Duration: each medication was injected subcutaneously 3 mo every 4 wk and primary endpoint readout 2 wk after the last dosage (week 10)	• FricTest - Response after scratching with FricTest: - Complete response—absence of a positive test response to the strong friction strength - Partial response—a reduction of 2 or more FricTest grades - No response-no reduction of FricTest grades • QoL using the DLQI	Clinical response (N/total)	Changes in DLQI (N/total)	• Adverse events were evaluated in all 61 patients • Serious adverse events: 1/19 patient with omalizumab 150 mg (underwent surgery due to an inguinal hernia) 1/21 patient with omalizumab 300 mg (acute cystitis) 1/21 patient with placebo (renal colic due to calculus of ureter) • Upper respiratory tract infection in 12/21 (63%), 6/21 (29%), and 8/21 (39%) in patients who received omalizumab 150 mg, omalizumab 300 mg, and	• Both omalizumab 150 and 300 mg gave a high rate of complete and partial responders, as well as an improvement of QoL										

			placebo, respectively
			• Other infections in 6/21 patients (32%), 2/21 patients (10%), and 2/21 patients (10%) in patients who received omalizumab 150 mg, omalizumab 300 mg, and placebo, respectively
			• Headache in 6/21 patients (32%), 9/21 patients (43%), and 10/21 patients (48%) who received omalizumab 150 mg, omalizumab 300 mg, and placebo, respectively
Omalizumab 150 mg			Complete response (8/18) Partial response (4/18) No response (6/18)
			Improved ≥ 4 points (13/18) Improved < 4 points (5/18)
Omalizumab 300 mg			Complete response (10/19) Partial response (1/19) No response (8/19)
			Improved ≥ 4 points (11/19) Improved < 4 points (8/19)
Placebo			Complete response (2/18) Partial response (1/18) No response (15/18)
			Improved ≥ 4 points (6/18) Improved < 4 points (12/18)

DLQI, Dermatology Life Quality Index; *N*, number; *N/A*, data not available in the study; *QoL*, quality of life; *SD*, symptomatic dermographism; *VAS*, visual analog scale.

**P* $< .01$ vs placebo.

TABLE VI. Characteristics of included nonrandomized controlled studies in patients with symptomatic dermatographism

			Results				
Study, year	Treatment methods	Devices and parameters	Reduction of wheals and flares		Subjective assessments	Side effects	Conclusion
A double-blinded, nonrandomized prospective study							
Cap et al 1985 ²⁹ N = 27; SD = 22	SD with cholinergic urticaria = 5 (dropout 3) (1)Ketotifen 24 mg/d (2)Placebo Duration: 1 mo for ketotifen, 1 mo for placebo, and the last month f or ketotifen, no washout time	Patients' self-assessment score with a 4-point scale: 0 = no symptoms 1 = weak 2 = medium 3 = strong			23 of 24 of patients showed marked improvement in itch and wheal formation with ketotifen - Wheal formation and itch were reduced statistically significantly (P < .001) as compared with placebo	- Weight gain in 1 patient - Fatigue in 3 patients - Dizziness in 1 patient - Loss of concentration in 1 patient - Acne intensified in 1 patient*	Ketotifen was of benefit in SD with minor side effects
Open label prospective studies							
Toth-Kasa and Husz 1987 ²⁸ N = 30	(1)Cinnarizine with pizotifen - First 2 d, cinnarizine 75 mg/d and pizotifen 0.5 mg/d - Third and fourth day, cinnarizine 75 mg/d and pizotifen 1 mg/d - From the fifth day, cinnarizine 75 mg/d and pizotifen 1.5 mg/d Duration: 6 wk - 13/30 patients received placebo for 1 wk before the treatment was given	- Dermographism test with 15-cm-long blunt end of a pencil (evaluated in only 13 patients who previously receive placebo) - Urticaria and itch symptoms	- Wheals and flare significantly decreased from baseline within the second (P < .05) and first week (P < .005) of the treatment, respectively 19 of 30 patients were completely protected from the development of wheals			N/A	The treatment was benefit in all cases. In some, patients were completely protected from the development of wheals
Logan et al 1989 ¹⁰ N = 14	- Whole-body irradiation with long-wave ultraviolet A in a Waldmann UV 6000 stand-up PUVA cabinet - Control area: the right side of the upper back was covered with aluminum foil during each treatment - Patients could take short-acting oral antihistamines as needed Duration: 3 times a week for 4 wk - Each week, doses of UVA were increased by 0.5-2.0 J/cm2 depending on the patient's tolerance	- Dermographometer - Measurement of wheal widths at 4 standard pressures: 0.8 × 105 Pa 3.5 × 105 Pa 6.7 × 105 Pa 9.4 × 105 Pa - Compared with treated area with control side of back - Measurement of the area of flare around the wheals 5 min after stroking by tracing onto a polythene sheet (N = 6) - Subjective estimation by each patient of the degree of whole-body pruritus by means of VAS (range 0-20)	- No significant reduction in wheal widths induced by PUVA during the 4-wk treatment period - There was no difference in the area of flare around the wheal on treated and untreated area	There was no significant reduction in the degree of pruritus (5/8 patients who had a decrease their pruritus at the end of treatment considered that the improvement was worthwhile. But in 4/5 patients, pruritus had relapsed to pretreatment levels within 3 mo of the end of treatment)	2/14 patients had prolonged erythema - No serious side effects were reported		
Kumar et al 2002 ³¹ N = 25	(1)Cetirizine 10 mg/d and betamethasone 2 mg/d (N = 7) (2)Cetirizine 10 mg/d and cyclophosphamide 50 mg/d (N = 9) (3)Cetirizine 10 mg/d (N = 9) Duration: 4 wk	- Dermograder - Decrease of the dermograder (using dermograder) - Number of complete protected from the development of wheals - Relapse rate	Drugs	Decrease of the dermograder (N/total)	Complete protected from the development of wheals (N/total)	- Cetirizine and betamethasone -7/7 patients had weight gain -4/7 patients developed acne -2/7 patients had cushingoid - Cetirizine and cyclophosphamide -1/9 patient reported drowsiness - Cetirizine -2/9 patients reported drowsiness - None had laboratory changes during the study	- Add-on oral corticosteroids or cyclophosphamide was more effective than cetirizine alone in controlling symptoms - Four-week supplementation was not enough for preventing relapse in case of drug withdrawal
			Cetirizine and betamethasone	3/7	7/7		
			Cetirizine and cyclophosphamide	0/9	9/9		
			Cetirizine	0/9	6/9		

Ayala and Nino 2003 ³⁰	N = 20 Desloratadine 5 mg/d Duration: 3 mo	The efficacy was evaluated based on symptoms (pruritus) and signs with the aid of dermatographometer at 6 standard pressures: 15.5 g/mm2 34.2 g/mm2 59.5 g/mm2 79.1 g/mm2 96.8 g/mm2 133.7 g/mm2	•16/20: complete relieve •3/20: moderate relieve •1/20: no change in SD	This study comprised 24 patients (20 demographic urticaria, 3 delayed pressure urticaria, and 1 heat contact urticaria) and headache was reported in 2 of 24 patients	Desloratadine was effective in patients with SD																				
Borzova et al 2008 ¹¹	N = 8 Narrowband ultraviolet B 3 times weekly and fexofenadine as needed (Before the study, patients received fexofenadine 180 mg/d. During post-treatment follow-up for 3 mo, patients took fexofenadine as needed) Duration: 6 wk	- Dermatographometer - Measurement of wheal widths at 3 pressures: 20 g/mm2 36 g/mm2 60 g/mm2 • Wheal and pruritus assessed by patient's VAS	<table><tr><th></th><th>Week 0 (mm)</th><th>Week 6 (mm)</th><th>P value[†]</th><th>N/A</th></tr><tr><td>VAS wheal</td><td>46</td><td>6.19</td><td>.008</td><td></td></tr><tr><td>VAS pruritus</td><td>57</td><td>25.75</td><td>.006</td><td></td></tr></table>		Week 0 (mm)	Week 6 (mm)	P value [†]	N/A	VAS wheal	46	6.19	.008		VAS pruritus	57	25.75	.006		• Narrowband UVB phototherapy was an effective second-line treatment for patients with SD						
	Week 0 (mm)	Week 6 (mm)	P value [†]	N/A																					
VAS wheal	46	6.19	.008																						
VAS pruritus	57	25.75	.006																						
Metz et al 2014 ³⁵	N = 7 Omalizumab, initial dose was varied (150 or 300 mg every 2-4 wk). If symptoms could not be controlled, titrate dose up to 150, 300, or 450 mg every 2-8 wk was performed. The minimum effective dose was 150-450 mg every 2-8 wk	• FricTest - Response after scratching with FricTest - Complete response: absence of a positive test response to the friction strength or absence of symptoms as assessed by patient global assessment - Significant improvement: 50% or more reduction in provocation thresholds or more than 50% improvement of symptoms - No response: a less than 50% reduction in provocation thresholds or improvement of symptoms	•6 of 7 patients had complete response •1 of 7 patient had significant improvement	• Cutaneous angioedema in 1 patient[‡]	• Omalizumab provides rapid and effective symptom relief in patients with SD																				
Toda et al 2011 ¹² (Case series)	N = 6 Ciclosporin (0.8-3.4 mg/kg/d) in addition to patients' current medications	• Dermatographometer - Wheal, flare, and itch response with 60 g/mm2 pressure • Clinical response by patients' self-assessment	<table><tr><td></td><td colspan="3"> • 1/6 patient: remission • 3/6 patients: clinical improvement • 2/6 patients: no benefit from the treatment (insufficient effects and/or side effects) </td></tr><tr><td>Case</td><td>Wheals</td><td>Flare</td><td>Itch</td></tr><tr><td>2</td><td>—</td><td>↓</td><td>↓</td></tr><tr><td>3</td><td>—</td><td>↓</td><td>—</td></tr><tr><td>4</td><td>—</td><td>—</td><td>↓</td></tr></table>		• 1/6 patient: remission • 3/6 patients: clinical improvement • 2/6 patients: no benefit from the treatment (insufficient effects and/or side effects)			Case	Wheals	Flare	Itch	2	—	↓	↓	3	—	↓	—	4	—	—	↓	• 1/6 patient felt epigastric distress • 1/6 patient had headache and nausea • No laboratory changes during the study were reported	• Oral ciclosporin may benefit in antihistamine-resistant patients with SD
	• 1/6 patient: remission • 3/6 patients: clinical improvement • 2/6 patients: no benefit from the treatment (insufficient effects and/or side effects)																								
Case	Wheals	Flare	Itch																						
2	—	↓	↓																						
3	—	↓	—																						
4	—	—	↓																						

N, Number; N/A, data not available in the study; PUVA, psoralen and ultraviolet-A; SD, symptomatic dermatographism; UV, ultraviolet; VAS, visual analog scale.

*Side effects were included in both SD and cholinergic urticaria.

[†]P < .05 was statistically significant.

[‡]Side effects were included in patients with SD, cholinergic urticaria, delayed pressure urticaria, cold urticaria, solar urticaria, and heat urticaria.

<10 years ago ($n = 3$).^{12,34,35} Among the RCTs, there were 134 (58.8%) female patients in 12 studies,^{7-9,17,19,21,23-27,34} and the gender of patients was not mentioned in 3 studies.^{13,20,22} The non-RCTs enrolled 48 (57.8%) female patients in 5 studies,^{10-12,28,31} and the gender of patients was not mentioned in 3 studies.^{29,30,35} The RCTs were performed in the United Kingdom ($n = 11$), Germany ($n = 2$), the United States ($n = 1$), and India ($n = 1$).^{7-9,13,17,19-27,34} The non-RCTs were performed in Germany ($n = 3$), Japan ($n = 1$), the United States ($n = 1$), the United Kingdom ($n = 1$), Italy ($n = 1$), and India ($n = 1$).^{10-12,28-31,35}

Of the 23 studies, 22 assessed treatment responses by provocation and/or threshold testing (objective assessment).^{7-13,17,19-28,30,31,34,35} Four instruments were used for this: (1) the HTZ dermatographometer (13 RCTs^{7-9,13,19-27} and 4 non-RCTs^{10-12,30}); (2) the dermograder (1 non-RCT³¹); (3) FricTest (1 RCT³⁴ and 1 non-RCT³⁵); (4) the dermatograph (1 RCT¹⁷); and (5) the blunt end of a 15-cm-long pencil (1 non-RCT²⁸). Subjective assessments by patients and/or physicians of the clinical response, sleep disturbance, and/or QoL were performed in 9 RCTs^{8,13,19,20,23-26,34} and 8 non-RCTs.^{10-12,28-31,35} It should be noted that studies (as shown in Tables IV-VI) used different devices and protocols for assessing disease activity, leading to difficulty in comparing the results of each study.

Of 23 studies, 12 studies assessed itch.^{8-11,20,23-26,28,29,34} Seven studies assessed itch by visual analog score (VAS).^{8,9,20,23-26} One study assessed by use of the Dermatology Life Quality Index (DLQI),³⁴ and 1 study assessed by a 4-point scale.²⁹ Three studies did not mention how itch was assessed.^{9,20} Sleep disturbance was assessed in 2 studies; however, the evaluation methods were not described and the studies did not provide information on the link between sleep disturbance that sleep disturbance was caused by itch or not.^{25,26}

Thirteen different treatments were investigated, namely, 1stAH₁, 2ndAH₁, AH₂, the combination of AH₁ with other drugs (AH₂, cyclophosphamide, oral betamethasone, and serotonin antagonist: pizotifen), and omalizumab with other treatments (ciclosporin, psoralen and ultraviolet A [PUVA], narrowband ultraviolet B [NBUBV], nifedipine, and topical clobetasol).^{7-13,17,19-31,34,35}

1stAH₁ showed variable efficacy in patients with SD, and they had significant side effects

Chlorpheniramine. Of the 7 RCTs (6 crossover studies,^{7,13,19-22} 1 parallel study²³), using the width of the dermatographometer-induced wheal as the outcome measure, that investigated the effects of chlorpheniramine alone, 3 studies demonstrated a significant reduction of wheal-and-flare reaction (chlorpheniramine 12 mg/day,²³ 16 mg/day^{7,19}). In contrast, no reduction of wheal size with chlorpheniramine was shown in 4 RCTs (chlorpheniramine 4 mg/day,²¹ 12 mg/day,²⁰ 16 mg/day,¹³ and 32 mg/day²²). Two studies also demonstrated reduced itch symptoms via patient self-assessments.^{20,23} One of these 2 studies did not report how itch was evaluated²⁰; the other study assessed itch by VAS.²³ The other 5 studies did not mention itch assessment.^{7,13,19,21,22}

Four^{7,19,20,23} of the 7 RCTs^{7,13,19-23} reported the rates of patients with side effects from chlorpheniramine. Of the 71 patients in these 4 RCTs,^{7,19,20,23} 5 patients (7.0%) reported side effects, namely, tiredness (2.8%), dry mouth (2.8%), and

aching legs (1.4%). One RCT reported drowsiness, but it did not provide the number of patients affected.¹³

Ketotifen. There were 3 studies (2 RCTs^{13,27} and 1 non-RCT²⁹) on ketotifen. Of the 2 RCTs (crossover) using the width of the dermatographometer-induced wheal as the outcome measure,^{13,27} one reported that ketotifen (2 mg/day) led to a better wheal-size reduction and resolution than the placebo.²⁷ The other RCT showed that ketotifen was ranked fourth out of the 8 antihistamines studied.¹³ Itch was not evaluated by either of the 2 RCTs, but it was reported in the non-RCT, which states that ketotifen (24 mg/day) demonstrated improvement in both itch and wheal formation via the patients' self-assessment scores for 23 of 24 patients with SD. Itch was assessed by a 4-point scale.²⁹

Mild sedation and increased appetite were observed in 4 of 24 patients (16.7%) in 1 RCT.²⁷ One non-RCT reported fatigue (3 patients), and weight gain, dizziness, loss of concentration, and acne in 1 patient each, in 36 SD and non-SD patients.²⁹

Other 1st AH₁. In 1 RCT (crossover), using the width of the dermatographometer-induced wheal at pressures 3650 and 7400 g/cm² as the outcome measure, hydroxyzine (75 mg/day) was more effective than chlorpheniramine in the reduction of wheal size and itching, with 29 of 33 patients (87.8%) showing reduced itch.²⁰ No data were available about how itch being measured.²⁰ Another RCT (crossover) reported that the combination of hydroxyzine (40 mg/day) and cimetidine (1600 mg/day) was the most effective SD treatment, as assessed in 12 patients by subjective evaluation of relative efficacy, followed by hydroxyzine (40 mg/day), cyproheptadine (16 mg/day), ketotifen (2 mg/day), trimeprazine (30 mg/day), promethazine (50 mg/day), mepyr-amine (150 mg/day), and chlorpheniramine (16 mg/day).¹³

One RCT (crossover) reported drowsiness (5 patients, 15.2%) and lack of concentration while driving (1 patient, 3.0%) in patients receiving hydroxyzine.²⁰ Another RCT (crossover) reported severe drowsiness in 4 patients (33.3%) and nightmares in 1 patient (8.3%) receiving trimeprazine.¹³

In all studies, 1stAH₁ were effective for SD and had good safety profiles

Cetirizine, acrivastine, ebastine, and desloratadine all showed benefits in studies on SD. Cetirizine (10 mg/day) was more effective than a placebo in 2 of 2 RCTs (crossover), using the width of the dermatographometer-induced wheal at pressures 17.5 to 95.5 g/mm² as the outcome measure,^{25,26} and in 1 non-RCT, using the width of the dermograder-induced wheal as the outcome measure, 6 of 9 patients (66.7%) were complete responders.³¹ The RCTs did not report safety outcomes.^{25,26} In the non-RCTs, 2 of 9 patients (22.2%) had drowsiness.³¹ Acrivastine (8 mg, 3 times a day) and ebastine (20 mg, single dose) were both more effective than a placebo in 1 RCT each (crossover), using the width of the dermatographometer- and dermatograph-induced wheal as the outcome measure, respectively.^{8,17}

Impairment of cognitive performance and mood assessment were not different between ebastine and a placebo.¹⁷ There were no side effects in the group with acrivastine.⁸ In 1 non-RCT with 20 patients, desloratadine (5 mg/day), using the width of the dermatograph-induced wheal as the outcome measure at 6 pressures (15.5, 34.2, 59.5, 79.1, 96.8, and 133.7 g/mm²), resulted in complete control in 16 patients (80%), whereas 2 reported headaches.³⁰

Monotherapy with an AH₂ was not effective for SD

The treatment of patients with SD with cimetidine was assessed by 4 RCTs (crossover), using the width of the dermatographometer-induced wheal as the outcome measure.^{7,19,21,22} Cimetidine dosages were 400,²¹ 1200,²² and 1600 mg/day.^{7,19} Three RCTs reported that cimetidine did not inhibit wheal-and-flare reactions,^{19,21,22} and among these, 1 RCT even reported clinical worsening, as determined by patients' assessments.¹⁹ One RCT reported that cimetidine was less effective for SD treatment than chlorpheniramine alone or than the combination of chlorpheniramine and cimetidine.⁷ As to side effects, 1 RCT reported itchy eyes in 1 patient.¹⁹

Adding an AH₂ increased the efficacy of treatment with sedating AH₁

The combination of chlorpheniramine and cimetidine. Four RCTs (crossover), using the width of the dermatographometer-induced wheal as the outcome measure, reported that the combination of chlorpheniramine and cimetidine was more effective than either drug alone for the reduction of wheal-and-flare reactions^{7,19,21,22} (chlorpheniramine 4 mg/day with cimetidine 400 mg/day,²¹ chlorpheniramine 16 mg/day with cimetidine 1600 mg/day,^{7,19} and chlorpheniramine 32 mg/day with cimetidine 1200 mg/day²²). In 1 RCT, 10% of patients complained of moderate drowsiness,¹⁹ whereas another RCT reported that no patient experienced any side effects.⁷

The combination of hydroxyzine and cimetidine. In 1 RCT (crossover), using the width of the dermatographometer-induced wheal at 3 pressures (3.5×10^5 , 6.7×10^5 , and 9.4×10^5 Pa) as the outcome measure, the combination of hydroxyzine (40 mg/day) and cimetidine (1600 mg/day) was significantly superior to hydroxyzine or other 1stAH₁ alone in wheal-size reduction and patients' rank order of efficacy.¹³ The only reported side effect of this combination was drowsiness.¹³

The combination of cetirizine and ranitidine. One RCT (crossover), using the width of the dermatographometer-induced wheal at pressures of 17.5 to 95.5 g/mm² as the outcome measure, showed that the wheal threshold for the combination of cetirizine (10 mg/day) and ranitidine (300 mg/day) group was significantly increased relative to a placebo.²⁶ However, there was no difference in patients' preferences for cetirizine with ranitidine and cetirizine with a placebo.²⁶

Omalizumab was effective in patients with SD

One RCT with 55 patients reported that omalizumab (150 and 300 mg, every 4 weeks for 3 months) reduced whealing thresholds, as assessed by the FricTest, and improved QoL, as measured by the DLQI. Seventy-two percent patients treated with 150 mg omalizumab and 58% patients treated with 300 mg omalizumab improved at least 4 points in the DLQI scale. The authors only reported the improvement of total DLQI scores. They did not mention details for each item of the DLQI such as the effect of treatment for items related to pruritus.³⁴

Other SD treatments

Eight other treatments were investigated in a total of 7 studies,^{9-12,24,28,31} all of which had low patient numbers and were unreplicated and/or uncontrolled. One non-RCT (n = 6) with ciclosporin (0.8-3.4 mg/kg/day in addition to patients' current medications), using the width of the dermatographometer-

induced wheal at pressures 60 g/mm² as the outcome measure, reported remission, clinical improvement, and no improvement in 1 patient (16.7%), 3 patients (50%), and 2 patients (33.3%), respectively.¹² Two patients reported side effects (33.3%), that is, headache and nausea (1 patient) and epigastric pain (1 patient).¹² One non-RCT, using the width of the dermatographometer-induced wheal at 4 pressures (0.8×10^5 , 3.5×10^5 , 6.7×10^5 , and 9.4×10^5 g/mm²) as the outcome measure, reported no significant reduction in wheal and pruritus in 14 patients during 4 weeks of PUVA therapy.¹⁰ Pruritus was assessed by VAS.¹⁰ Two patients (14.3%) reported that PUVA induced prolonged erythema.¹⁰ One non-RCT, using the width of the dermatographometer-induced wheal at 3 pressures (20×10^5 , 36×10^5 , and 60×10^5 g/mm²) as the outcome measure, reported a significant reduction of wheal width and pruritus by using NBUVB treatment with fexofenadine (180 mg/day), as needed, for all 8 patients with SD.¹¹ One small RCT (crossover), using the width of the dermatographometer-induced wheal at 4 pressures (2×10^5 , 5.87×10^5 , 9.75×10^5 , and 14.12×10^5 Pa) as the outcome measure, with nifedipine, divided into 2 trials, 1 with 15 mg/day and 1 with 30 mg/day, showed no significant reduction of wheal size or clinical improvement including itch by VAS score.²⁴ Five patients (23.8%) reported side effects, that is, hypotension (1 patient), dizziness with headache (3 patients), and intolerable headache with postural dizziness and edema (1 patient).²⁴ One RCT (parallel) with 6 patients, using a dermatographometer to assess wheal size, with topical clobetasol propionate (0.05%) showed decreased wheal width and itch.⁹ The evaluation method of itch was not mentioned.⁹ One non-RCT, using the width of the dermatographometer-induced wheal as the outcome measure, on cetirizine (10 mg/day) plus oral betamethasone (2 mg/day) or cyclophosphamide (50 mg/day) found both combinations to be effective in 7 of 7 and 9 of 9 patients, as compared with 6 of 9 patients treated with cetirizine 10 mg/day alone.³¹ The side effects of cetirizine/oral betamethasone were weight gain (7 patients, 100%; mean weight gain, 2.6 kg), acne (4 patients, 57.1%), cushingoid appearance (2 patients, 28.6%), and drowsiness (1 patient, 14.3%), whereas for the cetirizine/cyclophosphamide group, 1 patient (11.1%) reported drowsiness.³¹ One non-RCT, using the width of the 15-cm-long blunt end of the pencil-induced wheal as the outcome measure, on the combination of a serotonin antagonist (pizotifen, 0.5 mg/day in first 2 days, 1 mg/day in third and fourth day, and from sixth day to 6 weeks 1.5 mg/day) and 1stAH₁ (cinnarizine 75 mg/day) reported complete remission of SD in 19 of 30 patients after 6 weeks of treatment.²⁸

DISCUSSION

This is the first systematic review of the treatment options for patients with SD. Although SD is a common variant of physical urticaria, the number of treatment studies performed so far is low, as is the number of patients per study. Because of this and the high heterogeneity of reported studies, a meta-analysis of the efficacy and treatment options is not possible.

Our systematic review showed that most studies (15 of 23) were performed on AH₁,^{7,8,13,17,19-23,25-27,29-31} either alone or in combination: 8 on 1stAH₁^{7,13,19-23,27} and 6 on 2ndAH₁.^{8,17,25,26,30,31} The results of those studies support the first-line treatment recommendation by the EAACI/GA²LEN/

EDF/WAO and EAACI/GA²LEN/EDF/UNEV consensus guidelines on urticaria, namely, the daily use of a standard-dosed 2ndAH₁ rather than the 1stAH₁.^{1,18} The 1stAH₁ in the studies showed variable efficacy in patients with SD, and they had significant side effects. The latter confirms the well-established risk profile of 1stAH₁, with its central nervous system side effects and anticholinergic effects.³⁹⁻⁴² In contrast, the 2ndAH₁ in all studies were effective and demonstrated a good safety profile. As of now, there is no direct evidence to support that 2ndAH₁ differ in their efficacy when used to treat patients with SD. The only head-to-head study performed to far, with acrivastine and terfenadine,⁸ was excluded from this systematic review because terfenadine was withdrawn from the market due to cardiac arrhythmia. We did not find any studies investigating the guideline-recommended second-line treatment of SD: to increase the dose of 2ndAH₁ by up to 4 times.^{1,18} Well-designed RCTs to investigate and compare the efficacy of standard-dosed and higher than standard-dosed 2ndAH₁ by making use of threshold testing and disease-specific patient-reported outcome measures for the assessment of SD activity, impact, and control are needed and should be performed. Interestingly, none of the studies we analyzed reported information on the association of changes in wheal size with symptoms including itch. Moreover, none of the analyzed reports focused on itch reduction as the primary aim of the studies performed. Itch is the most debilitating symptom of SD and the most frequent reason for patients to seek medical help, in our experience. In the patients with SD treated at our urticaria centers of reference and excellence,⁴³ itch is the major driver of QoL impairment and sleep problems, and treatment that results in the control of itch leads to improved QoL and a reduction of sleep disturbance. The lack of focus on itch in the studies analyzed may be, at least in part, due to their age and the lack of validated questionnaires when they were conducted. The development and use of validated patient-reported outcome measures for SD in therapeutic trials and clinical practice are important unmet needs that must be addressed.

Four RCTs^{7,19,21,22} show that an AH₂ alone is not effective for SD. In contrast, the combination of AH₂ and AH₁ appears to increase the efficacy of AH₁. There are no studies that assessed the efficacy of low-dose doxepin, a tricyclic antidepressant with AH₁ activity in treating patients uncontrolled by conventional AH₁. AH₂ treatment is not recommended by the current version of the international urticaria guidelines, and the results of our systemic review provide no reasons to change this.

Omalizumab appears to be effective and safe in the treatment of AH₁-resistant patients with SD, as shown by 1 RCT and 1 non-RCT.^{34,35} Lower doses of omalizumab, that is, 150 mg once a month, may be as effective as 300 mg, the standard dose for chronic spontaneous urticaria, but more studies are needed to confirm this.⁴⁴

The other 8 treatments were only investigated in small studies, all of which were unreplicated, uncontrolled, or both.^{7-11,13,17,19-31} A topical corticosteroid was reported by 1 RCT with a small number of patients and a short duration.⁹ We do not recommend the use of topical corticosteroids for the treatment of patients with SD because of its potential long-term side effects. Two different doses of nifedipine (15 and 30 mg/day) compared with a placebo in the same RCT showed no significant difference in the reduction of wheal size, compared with the placebo.²⁴ Therefore, we also do not recommend the use of nifedipine for the treatment of SD. Ciclosporin, a recommended treatment

option for patients with SD who do not respond to AH₁,^{1,18} was only investigated by 1 non-RCT with 6 patients.¹² Therefore, further studies are needed to characterize the benefits of ciclosporin treatment for SD.

Because of the side effects of ciclosporin, especially in patients with chronic kidney disease and hypertension,⁴⁵ physicians should be cautious in using it as an additional treatment for AH₁-resistant patients with SD. As it is, no firm conclusions or recommendations can be made for the use of ciclosporin for SD or for any of the other treatments for which no RCT or larger and multiple trials are available, including PUVA therapy,¹⁰ NBUVB,¹¹ the combination of cetirizine plus oral betamethasone or cyclophosphamide,³¹ and the combination of pizotifen with cinnarizine.²⁸ Generally, the side effects of cyclophosphamide included dose-related chemical hemorrhagic cystitis and agranulocytosis.⁴⁶ As there are many other alternative treatments with better safety profiles, we see no circumstances where the benefit of cyclophosphamide justifies the risk or its use.

Our systematic review also revealed that new and better treatment options are needed for patients with SD. Recently, benralizumab, a humanized monoclonal anti-interleukin-5 receptor antibody, was shown to be effective in 1 patient with severe SD and concomitant severe allergic eosinophilic asthma.⁴⁷ Other promising treatment options that should be developed for SD include antibodies that target inhibitory mast cell receptors, interleukin 33, interleukin 25, or thymic stromal lymphopoietin, dupilumab, and histamine H₄ receptor antagonists.⁴⁸

In conclusion, this systematic review showed that the available studies on the treatments for patients with SD are heterogeneous, mostly single-center, usually old and small, and often unreplicated. This points to a high need for more and better studies. We suggest that 2nd AH₁ should be the first-line treatment. In uncontrolled cases, a combination of AH₁ and AH₂ may be tried. Alternatively, even though there is no evidence for its efficacy over the standard dosage, the up dosing of a 2ndAH₁ may be considered, based on the extrapolation of evidence from chronic spontaneous urticaria. Omalizumab should be added for patients if these treatments fail. Finally, new and better treatments for SD are needed, as are the development and use of robust and validated outcome measures for SD, including disease activity scores beyond the already available urticaria control test and provocation threshold testing.

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