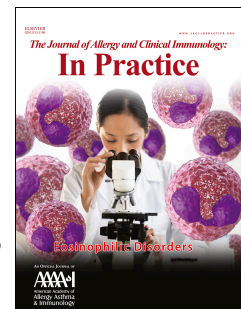


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ABSTRACT

Background: Delayed pressure urticaria (DPU) is characterized by recurrent erythematous and often painful swelling after the skin is exposed to sustained pressure. Treatment is challenging. Antihistamines, the first-line and only approved treatment, are often not effective.

Objective: To systematically review the treatment options for DPU.

Method: A literature search of electronic databases for all relevant articles published until April 29, 2019 was conducted using the search terms “delayed pressure urticaria” and “pressure urticaria”. This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses recommendations.

Results: Twenty-one studies (8 randomized controlled trials [RCTs], 10 retrospective cohort studies, and 3 open-label prospective studies) were included. Second-generation antihistamines (sgAHs) were effective in 3 RCTs. The combination of sgAHs and montelukast (2 RCTs) or sgAH and theophylline (1 non-RCT) was more effective than the sgAH alone. The disease improved with omalizumab (4 non-RCTs), sulphones (3 non-RCTs), oral prednisolone (1 RCT, 2 non-RCTs), intravenous immunoglobulin, and gluten-free diet (1 non-RCT each). There are no studies on up dosing of antihistamines over standard dosage in DPU.

Conclusion: Overall, the quality of studies on DPU is low. Due to the lack of other evidence, antihistamines remain the first-line therapy. Updosing of sgAHs could be considered in patients with uncontrolled symptoms based on the extrapolation of evidence from chronic spontaneous urticaria, even though there is no evidence of its efficacy over standard dosage. Addition of montelukast may be considered. Omalizumab or sulphones may be used in treatment-resistant patients. High-quality DPU studies should be conducted.

Highlights box:

What is already known about this topic?

Delayed pressure urticaria is a difficult-to-treat chronic inducible urticaria. Second-generation antihistamines (sgAHs) are often not effective.

What does this article add to our knowledge?

The quality of the existing studies in delayed pressure urticaria is low. Well-designed randomized controlled trials of up dosing antihistamines and omalizumab are needed.

How does this study impact current management guidelines?

Due to the lack of other evidence, sgAHs remain the first-line therapy. Up dosing of sgAHs or the addition of montelukast could be considered in uncontrolled cases. Omalizumab or sulphones may be used in treatment-resistant patients.

Keywords: Delayed pressure urticaria; Systematic review; Treatment

76 Abbreviations used

77 CIndU: Chronic inducible urticaria

78 CSU: Chronic spontaneous urticaria

79 DPU: Delayed pressure urticaria

80 IgE: Immunoglobulin E

81 IL: Interleukin

82 IVIG: Intravenous immunoglobulin

83 lb: Pound

84 NSAIDs: Nonsteroidal anti-inflammatory drugs

85 RCT: Randomized controlled trial study

86 sgAH: Second-generation H₁-antihistamine

87 TNF: Tumor necrosis factor

88

INTRODUCTION

Delayed pressure urticaria (DPU) is a subtype of chronic inducible urticaria (CIndU) that is characterized by recurrent erythematous and often painful swelling after the skin is exposed to sustained pressure. DPU is different from all other forms of chronic urticaria (except vibratory angioedema) in that it presents with deep dermal swellings but not with hives.¹ These swellings occur at skin sites of sustained pressure, rather than generalized, and they take several hours to develop, very different from other types of CIndU or CSU.¹ Mast cells in the deep dermis and subcutis are believed to be the key cellular drivers.² DPU skin lesions are characterized by a transient inflammatory infiltrate consisting mainly of neutrophils and eosinophils.^{2,3} Cutaneous levels of tumor necrosis factor (TNF)- α and interleukin (IL)-8 were shown to be increased in both lesional and nonlesional skin sites.⁴ DPU lesions take 4-6 hours to manifest and usually last for more than 24 hours.^{5,6} DPU is one of the least common subtypes of CIndU, occurring in less than 5% of all cases of CIndU.^{7,8} DPU may occur alone, along with other subtypes of CIndU, or together with chronic spontaneous urticaria (CSU).^{7,8} Disease activity of DPU can vary with time, and the reported mean duration ranges from 6 to 9 years.^{1,9,10}

DPU is diagnosed based on patient history and the results of skin provocation testing. Several different types of provocation tests are used in clinical practice. The “sandbag test” is performed by applying 15 pound (lb) of weight on the shoulder, forearm, or thigh for 15 minutes.⁵ Testing for DPU can also be performed with a dermatographic tester, which is a calibrated instrument (HTZ Limited, London, United Kingdom) with a spring loaded tip that is 0.9 mm in diameter. Its scale setting is 0 to 15, which equals to a range of tip pressures from 20 to 160 g/mm².^{11,12} For diagnosis of DPU, the dermatographic tester is set to 100 g/mm² of pressure and applied for 70 seconds at the scapular area.^{11,12} Another method of DPU testing involves the

use of a 2.5-4.5 kg weighted rod with a convex end that is applied on the forearm, thigh, or back for 15 min.¹³ For all tests, the reading time is 4-6 hours after the end of provocation testing, and the test is considered to be positive when erythematous skin swelling appears at a test site.¹¹⁻¹³ Current guidelines recommend dermatographometer testing or weighted rod testing, as they yield reproducible results and they allow for determination of individual trigger thresholds.¹³⁻¹⁵

All forms of chronic urticaria affect patient's quality of life, and DPU is no exception.¹⁶ In fact, DPU is known to be linked to very high levels of quality of life impairment, mainly because lesions are painful and they cause functional impairment.¹⁶ It restricts activities linked to exposure to pressure, such as riding a bicycle or performing manual labor. Choices in types of fitted clothing and shoes are also limited.¹⁰ The impact of DPU on quality of life occurs not only during or after performing activities that cause pressure, but also during or after daily routine activities, such as walking. DPU can also cause sexual impairment, which is also a diagnostic feature. Patients are recommended to avoid activities that might exacerbate the condition, such as carrying heavy objects and prolonged standing or sitting.¹⁰

The treatment of patients with DPU is challenging.^{1,13-15,17} Antihistamines, the mainstay therapy for all forms of chronic urticaria, are the recommended first-line DPU treatment according to current guidelines.¹⁵ Antihistamines at their own standard doses are often not effective in patients with DPU.¹⁸ As a result, other drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, sulfasalazine, dapsone, intravenous immunoglobulin (IVIG), and omalizumab, are frequently used in the management of DPU.^{6,9,19-22} To date, the outcome of treatments used in patients with DPU has not been systematically reviewed.

Accordingly, this comprehensive review was performed to investigate the efficacy of treatment options for patients with DPU by systematically searching for all available published literature. Both randomized controlled trials (RCTs) and non-RCTs were included.

METHODS

Search strategy and selection criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses recommendations (PRISMA).²³

A literature search of electronic databases (PubMed, OVID Medline, and EMBASE) for all relevant articles published until April 29, 2019 was conducted using the search terms “delayed pressure urticaria” and “pressure urticaria”. Our prespecified inclusion criteria were that the study 1) had to be an RCT, retrospective cohort study, or open-label prospective study; and, 2) had to provide information about the treatment efficacy of DPU. The reported efficacy could be the reduction in size and/or number of DPU skin lesions or changes in quality of life. Our only exclusion criterion was non-RCTs that reported on less than 5 DPU patients (to minimize the potential bias inherent to non-representative cases). Two independent reviewers (KK and NC) screened all titles/abstracts for eligibility. All potentially eligible studies were then reviewed again in full text by the same two reviewers (KK and NC). Determination of study eligibility needed to be confirmed by both reviewers. Any disagreement was resolved by consensus between reviewers.

Our search strategy yielded 2,673 potentially relevant publications (625 from OVID Medline, 1545 from EMBASE, and 503 from PubMed). After the exclusion of 356 duplicates, 2,317 publications underwent title and abstract review. At this stage, 2,290 articles were

excluded since they were case reports, retrospective cohort studies of less than 5 DPU patients, or review articles, which left 27 articles for a full-length article review. Four of those articles were later excluded because they did not report any outcome of interest. Three publications by Kontou-Fili, *et al.*^{18,24,25} reported data from the same group of patients. Therefore, we included only the original article²⁵ in our systematic review to avoid patient duplication. The remaining 21 studies were included in this systematic review.

Data extraction

The following data were independently extracted from each study by 2 reviewers (KK and NC): (i) first author's name and the publication year; (ii) study design; (iii) number of treated patients with DPU and control patients, if there were any; (iv) name of medication and route of administration; (v) dose and duration of medication; and, (vi) reported outcomes.

Assessment of the risk of bias and of the quality of the evidence

The risk of bias of the RCTs included in this systematic review was assessed by Cochrane Collaboration tool.²⁶ The quality of the evidence for each outcome was evaluated using the GRADE approach.²⁷ In brief, GRADE categorizes the quality of evidence into high, moderate, low, and very low, primarily based on the type of study performed (RCTs = high, non-RCTs = low). Studies are assessed for issues relating to limitations, inconsistency, indirectness, imprecision or publication bias, and the quality of evidence is adjusted accordingly.

RESULTS

The number of studies in DPU are limited and they show a balanced gender distribution.

In total, 21 studies were found to be suitable for inclusion in this systematic review. Of these, 8 were RCTs^{6,9,25,28-32} (3 of which were crossover studies) 10 were retrospective cohort

studies^{21,22,33-40}, and 3 were open-label prospective studies⁴¹⁻⁴³. All studies were conducted only in adult populations. There was a total of 332 patients, 291 of whom had DPU alone, and 41 had DPU and CSU. The RCTs included 166 DPU patients from three countries, i.e. the United Kingdom, Greece, and Italy.^{6,9,25,28-32} Among the RCTs, there were 78 (51.3%) female patients in seven studies; however, one study⁹ did not report the gender of the 14 participants investigated. The non-RCTs included 166 patients from 8 countries, i.e. the United Kingdom, the United States of America, Germany, Denmark, Greece, France, Japan, and Portugal.^{21,22,33-43} Among the non-RCTs, there were 75 (51%) female patients from 10 studies. Three non-RCTs^{22,38,39} did not report patient gender.

Among the studies in DPU, the risk of bias is moderate and the quality of evidence is low.

All RCTs except Vena, *et al.*³² (2006) had selection bias (see Table E1 in the Online Repository). Attrition bias presented in two RCTs by Vena, *et al.*²⁹ (1998) and Vena, *et al.*³² (2006). No reporting bias, performance bias, or detection bias was present in any of the RCTs. Based on the use of the GRADE approach²⁷, the quality of the majority of the included studies was low to very low with the exception of a few that were considered moderate (see Table E2 in the Online Repository).

Among the studies in DPU, assessment of the outcome of treatment is heterogeneous.

Skin provocation testing was performed to assess treatment response in all of the eight RCTs^{6,9,25,28-32}, and in 2 of the 13 non RCTs.^{22,34} Three RCTs^{6,9,31} used dermatographometer testing, 3 RCTs^{25,29,30} used 7-kg weight pressure testing, and 2 RCTs^{28,32} used steel rods (weighing 3.5 kg; diameter 15 mm). One non-RCT³⁴ used 15-lb weight pressure testing, and another non-RCT²¹ used weighted metal rods.

Subjective outcomes, such as the frequency and duration of swelling, the duration of the absence of symptoms, the presence of burning and pain sensation, and the ability to return to normal activities, were used in 4 of 8 RCTs^{6,29,31,32}, and in 13 of 13 non-RCTs.^{21,22,33-43}

Thirteen treatment options were studied, including antihistamines, antihistamines with montelukast, antihistamine with theophylline, antihistamine with NSAID, topical corticosteroids, oral corticosteroids, omalizumab, dapson, sulfasalazine, indomethacin, colchicine, IVIG, and a gluten-free diet. Table I and Table II, respectively, show a summary of the RCTs and non-RCTs included in our review.^{6,9,21,22,25,28-43}

Second-generation H₁-antihistamines (sgAHs) are effective in the treatment of patients with DPU.

RCT studies: Two RCTs, one employing cetirizine and one employing desloratadine, compared the efficacy of sgAHs against placebo.^{25,31} Cetirizine 10 mg three times a day was more effective than placebo for reducing the provocative area of DPU lesions, and also eosinophil counts as assessed by cytological skin window examination.²⁵ Details relating to the number of patients who responded, and the size of DPU lesion before and after treatment with cetirizine or placebo were not available. Moreover, the study did not compare with cetirizine 10 mg per day. Desloratadine 5 mg per day led to the absence of DPU lesions in 3 of 11 patients (27%).³¹ The mean diameter after treatment in the desloratadine group was 9.6 mm, which was significantly less than the mean diameter after treatment of 11 mm in the placebo group ($P < .05$).³¹

Non-RCT studies: Two non-RCTs investigated the effects of sedating antihistamines on DPU.^{33,34} One study reported that hydroxyzine (in combination with cimetidine) was not

effective for preventing induced DPU lesion development in any of the 13 DPU patients investigated.³⁴ Another study in chlorpheniramine alone and promethazine hydrochloride alone also showed no protection from induced DPU lesion.³³

There are no studies on the efficacy of up dosing antihistamines over standard dosage in DPU.

The combination of a sgAH with montelukast is more effective than treatment with a sgAH alone. The combination with theophylline may be more effective than treatment with a sgAH alone.

RCT studies: Nettis, *et al.*³⁰ studied the combined use of loratadine and montelukast and reported that the combination was more effective for preventing induced DPU lesions than loratadine alone. Another article by Nettis, *et al.*³¹ studied the use of desloratadine plus montelukast compared to desloratadine alone and placebo. The results were similar to their first study, as the combination of desloratadine and montelukast was the most effective combination for reducing the size of developing DPU lesions, followed by desloratadine alone and placebo.³¹

Non-RCT studies: Kalogeromitros, *et al.*⁴² studied the combination of cetirizine and theophylline and concluded that it was superior to cetirizine alone for reducing the number and size of DPU lesions and for subjective improvement.

There was no study of montelukast or theophylline alone in DPU.

The use of a topical corticosteroid and oral corticosteroid may be effective in the treatment of DPU.

RCT studies

Oral corticosteroids: Vena, *et al.*²⁹ (1998) studied the efficacy of oral prednisolone tapering for 7 weeks and reported a reduction in disease activity of 85.1% from baseline.

Topical corticosteroids: The prophylactic use of topical clobetasol propionate 0.05% for 6 weeks at the anterior thigh reduced the size of DPU lesions in 6 patients as compared to baseline, whereas placebo did not.²⁸ In a second study, clobetasol propionate 0.05% foam twice daily for 4 weeks significantly reduced the size of induced DPU lesion in 13 patients compared to baseline ($P = .001$), and placebo ($P = .0045$).³²

Non-RCT studies

Oral corticosteroids: Ryan, *et al.*³³ reported that the prophylactic use of oral prednisolone (30 mg/day) controlled DPU lesion completely in 3 of 15 patients (20%). In a second non-RCT, the prophylactic use of oral prednisolone at 40 mg/day for 3 days suppressed DPU lesions in all 14 studied patients (100%).³⁴ Morioke, *et al.*⁴⁰ studied the use of oral betamethasone as an on-demand treatment after unsuccessful treatment with antihistamine with or without montelukast, tranexamic acid, and cimetidine. The authors reported that this treatment was effective for improving DPU symptoms as demonstrated by the ability to discontinue the medication in 3 of 17 patients (17.6%), and to reduce the dose of medication used in 9 of 17 patients (52.9%).⁴⁰ The duration of oral betamethasone treatment ranged from 1 to 118 months.⁴⁰

There was no study of topical corticosteroids in the included non-RCTs.

Omalizumab may be effective in the treatment of patients with DPU.

Omalizumab was found to be effective in the treatment of DPU in all of the 4 studies performed, and all of those studies were non-RCTs. Metz, *et al.*²² showed that omalizumab reduced provocative thresholds as assessed by weighted metal rods, as well as disease activity as

assessed by patient global assessment in 8 of 8 DPU patients (100%). Another study by Metz, *et al.*³⁹ investigated the efficacy of omalizumab at doses of 150-600 mg every 2 to 4 weeks in 6 DPU patients – 5 of whom had concomitant CSU, and 1 had DPU alone. Omalizumab treatment resulted in complete response (i.e., $\geq 90\%$ improvement in symptoms without the need for concurrent use of antihistamines) in all DPU patients.³⁹ Ghazanfar, *et al.*³⁸ showed that omalizumab 150 mg every 2 weeks or 300 mg every 4 weeks for 12 months improved DPU symptoms as measured by patient global assessment in 3 of 5 patients (60%). Similarly, Pinto, *et al.*⁴³ reported that omalizumab 150 mg or 300 mg every 4 weeks for 2 to 38 months reduced disease activity as measured by the UAS7 in 7 of 7 of patients with coexisting CSU and DPU (100%).

Sulphones may be effective in the treatment of patients with DPU.

Sulphones were investigated in three non-RCTs – two studied dapsone, and one studied sulfasalazine.³⁵⁻³⁷ Dayani, *et al.*³⁵ studied 50-100 mg of dapsone alone for up to 18 months and reported complete response in all 5 patients (100%). Grundman, *et al.*³⁶ used 25-50 mg of dapsone (together with vitamin C) and reported that dapsone reduced symptoms in 24 of 31 patients (77.4%). Swerlick, *et al.*³⁷ showed that sulfasalazine treatment resulted in complete, near complete, or partial response in 15 of 17 patients (88.2%) based on reduction in DPU symptoms and the ability of patients to return to normal activities.

Other treatments are rarely assessed for their efficacy in DPU.

RCT studies: Dover, *et al.*⁹ showed that indomethacin was not more effective than placebo for reducing the size of DPU lesions or improving symptoms. Lawlor, *et al.*⁶ reported no significant differences in the number or size of DPU lesions in patients treated with colchicine or placebo. The sequential use of NSAIDs, nimesulide alone for 3 weeks followed by nimesulide

combined with an old sedating antihistamine (ketotifen) for 2 weeks, and then ketotifen alone for 2 weeks resulted in a reduction in disease activity of 93.1% as compared to baseline.²⁹

Non-RCT studies: Dawn, *et al.*²¹ studied the efficacy of high-dose IVIG treatment for up to 48 months and reported remission (absence of symptoms) or improvement in the frequency and duration of DPU lesions in 5 of 8 patients (62.5%). Bazex, *et al.*⁴¹ studied the effects of a gluten-free diet in DPU patients and reported clinical improvement in 6 of 7 patients (85.7%).

Remission is mentioned in 4 non-RCTs and 1 RCT.

Of these five studies,^{6,21,35,40,41} remission was clearly defined in only two studies.^{21,40} For IVIGs, patients who did not need any medications after discontinuation of IVIG for 6 months were defined as “patients in remission”.²¹ For oral betamethasone, the absence symptoms with non-corticosteroids therapy after discontinuation of oral betamethasone for 6 weeks were defined as remission.⁴⁰ Concerning studies that reported remission (all non-RCTs), dapsone, oral betamethasone, IVIGs, and gluten-free diet induced remission in 60% (3/5), 53% (9/17), 38% (3/8), and 14% (1/7) of DPU patients, respectively.^{21,35,40,41} Of 13 patients treating with colchicine for one week, only 1 patient had remission (8%).⁶ Given the low numbers patients in these studies and the lack of a clear definition of remission in most of them, no solid conclusion can be drawn.

DISCUSSION

This is the first systematic review of all available literature that is specific to the treatment of patients with DPU. Since DPU is a relatively rare condition, non-RCTs and case series of more than 5 patients were included in our analysis in addition to RCTs. Meta-analysis of the included studies could not be performed due to the broad range of interventions and

measured outcomes. In many studies, the efficacy of treatments was assessed by provocation and threshold testings (i.e., measuring the size of induced swelling reactions before and after treatment).^{6,9,22,25,28-32,34} However, subjective outcomes, such as painful, burning, and/or aching sensations, after exposure to a certain amount of pressure over a period of time (usually at 4-6 hours) were also measured.^{6,21,22,29,31-43}

The daily use of sgAHs remains the treatment of choice. Both RCTs in sgAHs, one employing cetirizine the other employing desloratadine, showed both medications to be effective for DPU, albeit only moderately and not in all patients.^{25,31} Even though there are no RCTs that have investigated the efficacy of up dosing of sgAHs over standard dosage in DPU, up dosing of sgAHs could be considered in patients with uncontrolled symptoms based on the extrapolation of evidence from chronic spontaneous urticaria.⁴⁴ Up dosing of sgAHs (evidence level 0, best practice recommendation) is recommended by the international guideline in DPU patients who do not improve with standard dose.¹⁵

The pathogenesis of DPU is still unclear but involves mast cell degranulation and a late-phase reaction,⁴⁵ in which mast cell mediators and the recruitment of inflammatory cells play an important role.⁴⁶ Histamine and its actions on histamine H₁ receptors are involved, but so are several other mast cell mediators including cysteinyl leukotrienes (leukotriene C₄, leukotriene D₄ and leukotriene E₄) and prostaglandins.⁴⁶ Even though histamine was released in the lesions⁴⁷, the unresponsiveness of DPU in some patients suggests that histamine may not play a major role in the pathogenesis of DPU.¹¹

Based on the results of this review, patients with DPU who are refractory to sgAHs should receive additional therapy with montelukast, omalizumab, or dapsone. Montelukast has a good safety profile, is of low cost, and it was demonstrated by two RCTs to improve the efficacy of

sgAH treatment.^{30,31} Omalizumab was reported to have high efficacy in 3 non-RCTs^{22,39,43} and to be low to moderately effective in one non-RCT.³⁸ Even though omalizumab has not been approved for DPU¹⁵ and the number of patients in the included studies was small, we believe that it may be considered as a treatment option in patients with DPU who do not respond to sgAHs based on its good safety profile and its good success rate in most studies.^{17,48} Moreover, it is also effective in other types of CIndU.^{17,48,49} There is a great need to perform double-blind RCTs to characterize the efficacy and safety of treatment with omalizumab in DPU. Ligelizumab, a novel anti-IgE monoclonal antibody that has recently been shown to be more effective than omalizumab in the treatment of patients with CSU,⁵⁰ should also be assessed for its efficacy in DPU by RCTs. Antolimab (anti-Siglec8), which was shown to inhibit mediator release in mast cells and to yield promising responses in patients with antihistamine-resistant CU, should also be further investigated.⁵¹

Dapsone was studied in two non-RCTs in recalcitrant DPU patients.^{35,36} Even though the results suggest that it is effective and none of the patients treated with dapsone in Dayani's study developed methemoglobinemia within 18 months.³⁵ Dose-dependent hemolysis is the most common side effect of dapsone which can lead to methemoglobinemia. Other major side effects include, agranulocytosis, peripheral neuropathy, and psychosis. Thus, the use of dapsone requires careful consideration.^{36,52} Recommended laboratory monitoring during dapsone usage includes complete blood count with differential every week for 4 weeks, and then every 2 weeks until week 12, and then every 3 to 4 months.⁵³ Reticulocyte count and methemoglobin levels should be monitored as clinically indicated.⁵³ Dapsone is not safe for use in patients with glucose-6-phosphate dehydrogenase deficiency.³⁶ Due to the better safety profile and the need for long-term prophylactic treatment, which is often for many years, we favor the use of omalizumab over

dapsone. When omalizumab is not available, dapsone treatment, early during the course of DPU, may be considered. In cases where dapsone is prescribed, repeated blood investigations are needed to monitor for the development of methemoglobinemia.

It should be noted that some studies included both 1) patients with DPU alone, and 2) patients with DPU and co-existing CSU. Interestingly, the treatment response to dapsone was higher among patients with DPU alone than among patients with DPU and co-existing CSU.³⁶ In contrast, similar responses between these two patient subtypes were observed in studies of omalizumab.^{39,43}

Efficacy of topical and systemic corticosteroids to prevent development of DPU lesion has been demonstrated by a few trials that included a small number of participants.^{28,32} However, DPU is a chronic disease⁹ and the long term use of corticosteroids is associated with several adverse effects, including skin thinning, telangiectasia, immunosuppression, suppression of the pituitary adrenal axis, osteoporosis, diabetes, obesity, hypertension, and cataracts.⁵⁴⁻⁵⁷ Therefore, routine use of corticosteroids for DPU is not encouraged.

DPU, in virtually all patients, goes into spontaneous remission, the reported duration of DPU ranges from 6 to 9 years.^{1,9,10} This needs to be taken into account in the design of studies on the efficacy of DPU treatment options and in the interpretation of their results. Also, DPU treatments may be disease modifying and may induce remission. The information on this, from the studies performed so far, is inconclusive, and future studies should assess the rates of disease remission of DPU treatments, by the use of clear definitions of remission and follow up periods of sufficient duration.

It should be once again noted that the overall quality of the studies included in this review was low, so our results should be interpreted with caution and consideration. This review shows which treatments might offer opportunities for success in RCTs with a well-defined outcome, i.e. provocation threshold testing. As of now, however, it is largely unclear how induced swellings and trigger thresholds translate to categories of disease activity (mild vs moderate vs severe) and how changes in induced swellings and trigger thresholds reflect changes in DPU disease activity in real life (the minimal clinically important difference, MCID, for example). Future studies should aim to provide this information. Also, disease activity scores for DPU and other CIndUs should be developed and used to assess disease activity and treatment response in addition to the use of provocation and threshold testing.

DPU is difficult to treat and patients are often disappointed with what we can offer to them. Thus, there is an urgent need for new good studies on the treatment of DPU. Due to the low prevalence of DPU, high-quality studies will require a multicenter approach, ideally within the network of Centers of Reference and Excellence in Urticaria (UCAREs) or a similar multicenter collaboration.⁵⁸ Future developments of treatment for patients with chronic urticaria should include clinical trials of DPU since better therapies are urgently needed. Given the low prevalence of DPU and, therefore, limited number of patients, the implementation of a double-blind placebo-controlled trial design may be difficult, but future studies should make use of patient randomization and clear subjective and objective outcomes.

The limitations of this review include (i) the relatively small number of studies that focused on the efficacy of treatments for DPU; and, (ii) the low quality of the majority of available studies. There is marked heterogeneity relative to what treatments were investigated

399 and how treatment responses were assessed. Therefore, solid recommendations regarding how
400 patients with DPU should be treated cannot be drawn from this review.

401 In conclusion, we suggest sgAHs as the first-line treatment for DPU. If symptoms cannot
402 be controlled, up dosing of sgAHs and the addition of montelukast may be considered.
403 Omalizumab or dapsone may be used in patients with refractory DPU.

404

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TABLE I. Characteristics of included randomized controlled trials studies

Study, year	N	Treatment (Method of drug administration)	Dosage	Duration	Devices†			Results Parameter				Conclusion		
					D	W	R	Number of DPU lesions	Size of DPU lesions	Subjective assessment	Skin biopsy/ cytologic examination			
Dover, et al., 1988⁹ (crossover)	14	Indomethacin vs. placebo	Wk1 indomethacin 25 mg tid or placebo Wk2 washout period Wk3 Placebo or indomethacin 25 mg tid	3 wk	✓			N/A	N/A	N/A	N/A	No significant subjective improvement or reduction in area of DPU lesions during indomethacin use compared to placebo, except slightly improved in 5 severe cases		
Lawlor, et al., 1989⁶ (crossover)	13	Colchicine vs. placebo	Wk1 colchicine 0.5 mg bid or placebo Wk2 drug free period Wk3 Placebo or colchicine 0.5 mg bid	3 wk	✓			Mean increase of 2.75 DPU lesions during taking colchicine (<i>P</i> > .2)	N/A	5/13: colchicine was better 1/13: placebo was better 6/13: no difference 1/13: complete remission after first visit	N/A	No significant differences in number of DPU lesions or diameter of DPU lesions between colchicine and placebo		
Kontou-Fili, et al., 1991²⁵ (crossover)	11	Cetirizine vs. placebo	Wk1 cetirizine 10 mg every 8 hours or placebo Wk2-3 drug free Wk4 placebo or cetirizine 10 mg every 8 hours	4 wk		✓		N/A	N/A	N/A	Skin window cytologic examination showed significant reduction in eosinophils (<i>P</i> = .0029) in cetirizine group compared to placebo.	Significant reduction in area of DPU lesions with cetirizine treatment compared to baseline (<i>P</i> = .0051), and to placebo (<i>P</i> = .009)		
Barlow, et al., 1995²⁸	6	Clobetasol propionate (0.05%) ointment vs. placebo (prophylaxis use)	Clobetasol propionate (0.05%) ointment OD at anterior thigh (n=6) Placebo OD at the opposite anterior thigh (n=6)	6 wk of treatment and 4-8 wk of follow up			✓	N/A	Median of differences in areas of DPU lesions (mm ²)			N/A	Skin biopsy showed no significant difference between the corticosteroids and ointment base-treated sites in terms of T lymphocytes, neutrophils, eosinophils, monocytes, macrophages, and cells expressing the leukocyte integrins.	Significant decrease in area of DPU lesions compared with baseline at day 3, week 6, and during the follow-up period
									Day3 vs. baseline	Wk6 vs. baseline	Follow-up period vs. baseline			
									Corticosteroids: -862.8 (<i>P</i> = .036) Placebo: -434.0 (<i>P</i> = .142)	Corticosteroids: -626.9 (<i>P</i> = .036) Placebo: -417.1 (<i>P</i> = .208)	Corticosteroids: -492.1 (<i>P</i> = .036) Placebo: -360.5 (<i>P</i> = .142)			

TABLE I. Characteristics of included randomized controlled trials studies (continued)

Study, year	N	Treatment (Method of drug administration)	Dosage	Duration	Devices†			Results Parameter				Conclusion		
					D	W	R	Number of DPU lesions	Size of DPU lesions		Subjective assessment		Skin biopsy/ cytologic examination	
Vena, <i>et al.</i> , 1998 ²⁹	40	Nimesulide and ketotifen vs. prednisolone alone (prophylaxis use)	Wk1-3 Nimesulide 100 mg OD Wk4-5 Nimesulide 100 mg OD + ketotifen 2 mg OD Wk6-7 ketotifen 2 mg bid (n=N/A)	7 wk		✓		N/A	N/A		Average disease activity reduction from baseline = 93.1% in nimesulide and ketotifen group = 85.1% in prednisolone group (<i>P</i> = .09)	N/A	No statistical difference was observed between groups for size of DPU lesions [§] (<i>P</i> = .54) or disease activity.	
			Prednisolone Wk1-3 40 mg OD Wk4-5 30 mg OD Wk6-7 20 mg OD (n=N/A)											
Nettis, <i>et al.</i> , 2003 ³⁰	20	Loratadine plus montelukast vs. loratadine alone	Loratadine 10 mg plus montelukast 10 mg OD (n=10)	15 days		✓		N/A		Loratadine +montelukast N (%)	Loratadine, N (%)	N/A	N/A	Montelukast plus loratadine was significantly more effective than loratadine alone (<i>P</i> < .05).
									Total suppression [#]	8/10 (80%)	2/10 (20%)			
									Moderate response [#]	1/10 (10%)	1/10 (10%)			
									Mild or no response [#]	1/10 (10%)	7/10 (70%)			
			Loratadine 10 mg OD (n=10)											

TABLE I. Characteristics of included randomized controlled trials studies (continued)

Study, year	N	Treatment (Method of drug administration)	Dosage	Duration	Devices†			Results Parameter								Conclusion	
					D	W	R	Number of DPU lesions	Size of DPU lesions			Subjective assessment			Skin biopsy/ cytologic examination		
Nettis, <i>et al.</i> , 2006 ³¹	36	Desloratadine plus montelukast vs. desloratadine alone vs. placebo	Desloratadine 5 mg plus montelukast 10 mg OD (n=12)	2 wk	✓			N/A		Desloratadine + montelukast	Desloratadine	Placebo		Desloratadine + montelukast	Desloratadine	N/A	● Significant reduction in mean diameter of DPU lesions in the treatment group (desloratadine plus montelukast and desloratadine group) compared to placebo. ● Significant reduction in mean diameter of DPU lesions and clinical parameters in the desloratadine plus montelukast group compared to desloratadine alone.
			Desloratadine 5 mg plus placebo OD (n=11, dropout=1)						Mean diameter after treatment (mm)	5	9.6	11.8	↓mean TSS [‡] ↓mean pruritus score [‡] ↓mean erythema score [‡] ↓mean edema score [‡] ↓number of episodes score [‡]	97.2% 70.8% 66.7% 73.9% 61.1%	41.1% 53.9% 34.8% 36.4% 42.2%		
			Placebo alone OD (n=11, dropout=1)						Patients with total disappearance of DPU lesions, N (%)	10/12 (83%)	3/11 (27%)	N/A					
Vena, <i>et al.</i> , 2006 ³²	26	Clobetasol propionate 0.05% in thermophobic foam vs. placebo (prophylaxis use)	Twice daily at the most affected area and at a target area where a pressure challenge test was performed (n=13)	4 wk			✓	N/A	Pressure challenge test area lesions size (cm ²), mean ± SD			● Clobetasol foam reduced erythema score [‡] 65% from baseline (P = 0.001) ● Similar modifications were also observed for the edema and itching scores			N/A	● Clobetasol propionate 0.05% in thermophobic foam is effective for short-term treatment of DPU. ● No significant changes in plasma levels of ACTH, in cortisol, or in other safety parameters were observed in either study group.	
										Baseline	Wk4						
			Clobetasol foam							144 ± 141	21 ± 34.3 ^{ab}						
			Placebo foam							201 ± 198	216 ± 198						
									^a P = .001, Wilcoxon signed ranks test, comparison with baseline values ^b P = .0045, Mann–Whitney U test, comparison with placebo values								

ACTH, Adrenocorticotrophic hormone; CM, centimeter; DPU, delayed pressure urticaria; MM, millimeter; N, number; N/A, data not available in the study; SD, standard deviation; Wk, week

†Devices: D = dermatographometer; W = 7 kg weight; R = 1.5 cm steel rod weighing 3.5 kg (diameter 15 mm).

‡Pressure testing results were graded using a 4-point scale: 3 = no response; 2 = mild response; 1 = moderate response; 0 = severe response.

#Results were graded using a 4-point scale: 3 = no response; 2 = mild response; 1 = moderate response; 0 = severe response.

‡TSS score was graded using a 4-point scale regarding erythema, edema, and pruritus: 0 = none; 1 = mild; 2 = moderate; 3 = severe, and by the decrease in the number of separate urticarial episodes: 0 = no episode; 1 = one episode; 2 = two or three episodes; 3 = more than three episodes.

¶Erythema, edema, and itching were graded using a 5-point scale: 0 = no signs to 4 = severe signs.

TABLE II. Characteristics of non-randomized controlled trial studies of 5 or more DPU patients

Study, year	Method (N, treatment, dosage, and duration) (Method of drug administration)	Devices for diagnosis	Results parameter	Results			Conclusion
Retrospective cohort study							
Ryan, et al., 1968 ³³	N: 15 - chlorpheniramine maleate 8 mg every 6 hr or promethazine hydrochloride 50 mg every 8 hr, n=15 - prednisolone 30 mg/day, n=N/A - trasylol (proteinase inhibitor) intravenous (iv) 50,000 units 2 hourly*3 doses, n=5 - e-amino-caproic acid iv 10 mL., n=4 - hydroxyethylrutoside 250 mg QID, n=4 Duration: 18 months (prophylaxis use)	• 15 pound (lb) weight	• Symptoms of DPU (number of DPU lesions, depth of DPU lesions, painful lesions)	• Chlorpheniramine maleate and promethazine hydrochloride did not relieve the symptoms. • Prednisolone completely controlled DPU symptoms in 3 patients. • Trasylol led to controlling of DPU symptoms, reduction in depth of DPU lesions, and no response in 2, 3, and 2 patients, respectively. • E-amino-caproic acid inhibited DPU lesions in 3/4 patients. • Hydroxyethylrutoside, when combined with oral chlorpheniramine, controlled DPU lesions in 1/4 patients.			• DPU is unaffected by antihistamine, but it is controlled by corticosteroids.
Sussman, et al., 1982 ³⁴	N: 17 (14=DPU and CSU, 3=DPU alone) Treatment consists of 3 protocols (1) antihistamine (hydroxyzine 100 mg/day and cimetidine 1,200 mg/day) (2) aspirin 3,900 mg/day (3) prednisolone 40 mg/day Duration: 3 days for each protocol with washout period for 3 to 10 days (prophylaxis use)	• 15 lb weight	• Photographs • Patient's symptom diaries: description of induced lesions as followed • 15 lb weight for pressure challenge test CSU lesions: superficial pruritic lesion DPU lesions: deep painful, but not pruritic lesion		Response to pressure challenge test (n/total)	Positive clinical response (n/total)	• DPU was controlled with prednisolone or NSAID, but not with antihistamine.
				Hydroxyzine and cimetidine	Couldn't suppress (11/11)	CSU lesions (13/13) DPU lesions (0/13)	
				NSAID (aspirin)	Could suppress (6/6)	CSU lesions (0/10) DPU lesions (8/10)	
				Prednisolone	Could suppress (12/12)	CSU lesions (14/14) DPU lesions (14/14)	
Dayani, et al., 1992 ³⁵	N: 5 Dapsone 50-100 mg/day during treatment and 50 mg on alternate days-50 mg/day during maintenance Duration: follow-up period up to 18 months	• Glass sphere pressure test (weight N/A)	• Clinical response assessed by physicians	• Dapsone led to clearance of DPU lesions in all patients. • After discontinuing dapsone, DPU lesions appeared in 4/5 patients. However, after reintroduction of dapsone, all DPU lesions cleared up.			• Dapsone might be a successful treatment in DPU. • No significant side-effects were recorded.
Dawn, et al., 2003 ²¹	N: 8 High-dose intravenous immunoglobulin 2 g/kg/dose Duration: 1-6 infusions up to over 8 months, median follow-up period was 22 months (range: 12-48 months)	• N/A	• Clinical signs • DPU lesion episodes • Number and severity of DPU lesions pre- and post-treatment	• 3/8 (37.5%) achieved remission* • 2/8 (25%) improved* • 3/8 (37.5%) unchanged*			• Intravenous immunoglobulin induced remission or improved symptoms in 5/8 (62.5%) patients with DPU.
Morioke, et al., 2010 ⁴⁰	N: 17 Antihistamine with or without montelukast, tranexamic acid, and cimetidine with subsequently oral betamethasone 0.25-1.5 mg/day if antihistamine was not effective Duration: duration of receiving oral betamethasone ranging from 1-118 months. (on demand use)	• A rod with weights of 4 kg/1.5 cm ²	• Clinical response and the need for medication	All 17 of 17 patients required subsequent dose of oral betamethasone • 3/17 (17.6%) achieved cure [§] • 9/17 (52.9%) achieved remission [§] • 5/17 (29.4%) were in amelioration [§]			• A small amount of corticosteroids was effective for controlling delayed pressure urticaria.

TABLE II. Characteristics of non-randomized controlled trial studies of 5 or more DPU patients (continued)

Study, year	Method (N, treatment, dosage, and duration) (Method of drug administration)	Devices for diagnosis	Results parameter	Results	Conclusion
Retrospective cohort study					
Grundmann, et al., 2011³⁶	N: 31 (15=DPU and CSU, 16=DPU alone) Wk1 – 25 mg of dapsone + 1 g vitC Wk2 – 50 mg of dapsone + 1 g vitC Wk3 – 100 mg of dapsone + 1 g vitC Wk4 and beyond – 150 mg of dapsone + 1 g vitamin C Duration: 9.7+5.2 weeks	• N/A	• Subjective assessment using 11-point numeric scale (NRS11)[#] • Laboratory monitoring - G6PD deficiency and CBC screening were performed prior to receiving dapsone. - Met-Hb was monitored during the study.	• 24 out of 31 patients with DPU had a very good[#] or good response[#] to dapsone • The treatment response to dapsone was higher among DPU patients without accompanying CSU than among patients with CSU (93% vs. 63%, $P = .05$)	• Dapsone showed good therapeutic benefit. • No significant effects were found related to Met-Hb elevation.
Metz, et al., 2014²²	N: 51 (8=DPU) Omalizumab 150 mg every 4 weeks or 300 mg every 4 weeks or 225 mg every 2 weeks Duration: 2-4 weeks	• Weighted metal rods (Weight N/A)	• Size of DPU lesions by weighted metal rods • Patient global assessment	• 7/8 = complete response[†] • 1/8 = significant improvement[†]	• Omalizumab might be effective in DPU.
Metz, et al., 2014³⁹	N: 25 (5=DPU and CSU, 1=DPU alone) Omalizumab ranging from 150-600 mg every 2 to 4 weeks Duration: at least 3 months	• N/A	CSU cases Urticaria activity score (UAS7) • Complete response: 90% or more reduction in UAS7 DPU alone cases • Complete response: A reduction in the trigger strength by 90%, and reduction in disease activity as measured by patient history	• 6/6 = complete response	• Omalizumab was a safe and effective option for treatment of chronic urticaria patients who previously benefited from this drug and showed relapse of symptoms.
Swerlick, et al., 2015³⁷	N: 17 Sulfasalazine 2-4 g/day Duration: follow-up period up to 120 months	• 10 lb of bottled water or canned goods	• DPU symptoms • Ability to perform normal activities	• 7/17 = complete response[‡] • 4/17 = near complete response[‡] • 4/17 = partial response[‡] • 2/17 = N/A	• Sulfasalazine was a low cost and effective treatment for DPU. • No complication or reported toxicity for chronic use as long as 120 months.
Ghazanfar, et al., 2016³⁸	N: 154 (5=DPU) Omalizumab 150 mg every 2 weeks or 300 mg every 4 weeks Duration: 12 months	• N/A	• Reduction in symptoms by physician's global assessment	• 3/5 = had a complete[¶] or almost complete response[¶] to treatment	• Omalizumab might be effective in DPU.

TABLE II. Characteristics of non-randomized controlled trial studies of 5 or more DPU patients (continued)

Study, year	Method (N, treatment, dosage, and duration) (Method of drug administration)	Devices for diagnosis	Results parameter	Results	Conclusion
Open labeled prospective study					
Bazex, et al., 1994⁴¹	N: 7 Gluten-free diet, no dosage available Duration: 13 months	• 6.75 kg weight	• Clinical response as assessed by physicians	• In 6 patients, dramatic results were obtained within 4 to 10 days, but with a recurrence of DPU symptoms after gluten ingestion in 5 patients. • Spontaneous remission was noted in 1 patient.	• Gluten-free diet improved DPU symptoms.
Kalogeromitros, et al., 2005⁴²	N: 23 Period 1 (6 months) - cetirizine (10 mg OD) and theophylline (200 mg BID) Period 2 (1 month) - a wash-out under rescue medication Period 3 (5 months) - cetirizine (10 mg OD) plus placebo (BID) Duration: 12 months	• 5.5 kg weight	• Number of DPU lesions VAS (visual analog scale) score from both patient and physician • Size of DPU lesions VAS (visual analog scale) score from both patient and physician • Subjective assessment - 11-point treatment effectiveness score (TES) [†] - patient's burning/pain sensation scoring [‡]	During the treatment period, theophylline lead to • Significant improvement in burning/pain scoring after 1 and 2 months • Significant improvement in VAS, TES, and burning/pain scoring after 3 months • Significant improvement in VAS and TES after 4 and 5 months	• The addition of theophylline resulted in statistically significant improvement over cetirizine alone by 2 months, and improvement continued for the duration of treatment.
Pinto, et al., 2017⁴³	N: 13 (7=concurrent DPU and CSU) Omalizumab 150 mg every 4 weeks or 300 mg every 4 weeks Duration: 2-38 months	• N/A	Urticaria activity score (UAS7) • Complete response: UAS7 = 0 • Partial response: UAS7 ≤ 28 • No response: UAS7 > 28	• 2/7 = complete response • 5/7 = partial response	• Omalizumab might be effective in DPU.

BID, two times a day; *CBC*, complete blood count; *CSU*, Chronic spontaneous urticaria; *DPU*, delayed pressure urticaria; *G*, gram; *G6PD*, Glucose-6-phosphate dehydrogenase; *Hb*, hemoglobin; *Hr*, hour; *KG*, kilogram; *Met*, methemoglobinemia; *MG*, milligram; *N*, number; *N/A*, data not available in the study; *NSAID*, Nonsteroidal anti-inflammatory drug; *OD*, once a day; *QID*, 4 times a day; *Wk*, week

*Remission: absence of symptoms with no requirement for corticosteroids, antihistamine, or other medication for a minimum of 6 months. Improved: reduction in frequency and duration of swellings as recorded by patients' diaries compared with pretreatment, and no further requirement for corticosteroids. Unchanged: no improvement or transient improvement of symptoms and no reduction in dose of corticosteroids.

§Cure: patients were able to discontinue all treatments. Remission: patients continued treatments without oral corticosteroids. Amelioration: patients continued treatments, including oral corticosteroids.

#NRS11: 0-3 = very good treatment; 4-6 = good response; 7-10 = poor response. Success was defined as a very good or good treatment response.

†Complete response: absence of DPU lesions after respective provocation testing 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 significant improvement: less than 50% reduction in provocation thresholds or improvement of symptoms.

‡A complete response was defined as return to normal activity with no evidence of DPU signs or symptoms. Near complete response indicated minimal activity and functional impact. A partial response was marked by an unquestionable decrease in disease activity, but persistent functional impact of disease.

μComplete or almost complete response: ≥ 90% reduction of symptoms. Partial response: reduction of symptoms between 30% and 89%. No response or a limited response: reduction of symptoms of < 30%.

□TES 11-point treatment effectiveness score: 0 = very severe symptoms to 10 = asymptomatic.

‡Burning/pain sensation scoring using 4-point scale: 0=absent; 1=mild; 2=moderate; and, 3=severe

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TABLE E1. Quality and risk of bias assessment of included randomized controlled trials studies

Study, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Dover, et al., 1988⁹ (crossover)	Unclear	Unclear	No bias	No bias	No bias	No bias
Lawlor, et al., 1989⁶ (crossover)	Unclear	Unclear	No bias	No bias	No bias	No bias
Kontou-Fili, et al., 1991²⁴ (crossover)	Unclear	Unclear	No bias	No bias	No bias	No bias
Barlow, et al., 1995²⁷	Unclear	Unclear	No bias	No bias	No bias	No bias
Vena, et al., 1998²⁸	Unclear	Unclear	No bias	No bias	Present bias 11/40 patients (27.5%) lost to follow-up	No bias
Nettis, et al., 2003²⁹	Unclear	Unclear	No bias	No bias	No bias	No bias
Nettis, et al., 2006³⁰	Unclear	Unclear	No bias	No bias	No bias	No bias
Vena, et al., 2006³¹	No bias	No bias	No bias	No bias	Present bias 6/26 patients (23%) lost to follow-up	No bias

TABLE E2. Summary of medication used in all randomized controlled trials (RCT) and non-RCT studies with the level of evidence of supporting study according to the GRADE system

Medication	Outcome measurement	Efficacy [#]	Number of studies	Results	Quality of evidence [†]						Reference, year
					LIM	INC	IND	IMP [*]	PB ^{**}	Quality	
Antihistamines											
Antihistamine alone	Provocation testing by 7 kg weight	+	2	One study showed significant reduction in size of DPU lesions and eosinophil count using cetirizine compared to placebo. One study showed that desloratadine was more effective for reducing the size of DPU lesions compared to placebo.	Not serious	N/A	Not serious	N/A	N/A	Moderate	Kontou-Fili, <i>et al.</i> , 1991 ²⁴ Nettis <i>et al.</i> , 2006 ³⁰ (RCTs)
	Subjective assessment	-	2	One study showed no improvement in DPU lesions using chlorpheniramine maleate alone, and promethazine hydrochloride alone. One study showed no improvement in DPU lesions using the combination of hydroxyzine and cimetidine.	Serious	Not serious	Not serious	N/A	N/A	Very low	Ryan, <i>et al.</i> , 1968 ³² Sussman, <i>et al.</i> , 1982 ³³ (non-RCTs)
Antihistamine + montelukast	Provocation testing by 7 kg weight	+	2	One study showed significant reduction in size of DPU lesions using the combination of loratadine and montelukast compared to loratadine alone. One study showed significant reduction in size of DPU lesions using the combination of desloratadine and montelukast compared to desloratadine alone.	Not Serious	Not serious	Not serious	N/A	N/A	Moderate	Nettis, <i>et al.</i> , 2003 ²⁹ Nettis <i>et al.</i> , 2006 ³⁰ (RCTs)
Antihistamine + theophylline	Subjective assessment	+	1	One study showed that the combination of cetirizine and theophylline led to improvement in DPU lesions and subjective assessment.	Not serious	N/A	Not serious	N/A	N/A	Very Low	Kalogeromitros, <i>et al.</i> , 2005 ⁴¹ (non-RCTs)
Corticosteroids											
Topical corticosteroids	Provocation testing by weighted rod	+	2	Two studies showed significant reduction in size of DPU lesions using clobetasol propionate 0.05% ointment and foam compared to placebo ³¹ and baseline ^{27,31} as a prophylaxis.	Serious	Not serious	Not serious	N/A	N/A	Low	Barlow, <i>et al.</i> , 1995 ²⁷ Vena <i>et al.</i> , 2006 ³¹ (RCTs)
Oral corticosteroids	Subjective assessment	+	3	Three studies showed significant improvement in DPU lesions after oral corticosteroids use as a prophylaxis ^{32,33} and as treatment. ³⁹	Serious	Not serious	Not serious	N/A	N/A	Very Low	Ryan, <i>et al.</i> , 1968 ³² Sussman, <i>et al.</i> , 1982 ³³ Morioka, <i>et al.</i> , 2010 ³⁹ (non-RCTs)
	Provocation testing by 7 kg weight	-	1	One study showed no significant reduction in disease activity compared to baseline after oral corticosteroids use as a prophylaxis.	Serious	N/A	Not serious	N/A	N/A	Low	Vena, <i>et al.</i> , 1998 ²⁸ (RCTs)

TABLE E2. Summary of medication used in all randomized controlled trials (RCT) and non-RCT studies with the level of evidence of supporting study according to the GRADE system (continued)

Medication	Outcome measurement	Efficacy [#]	Number of studies	Results	Quality of evidence [†]						Reference, year
					LIM	INC	IND	IMP*	PB**	Quality	
Omalizumab											
Omalizumab	-Provocation with weighted rod -Subjective assessment	+	4	Four studies showed that omalizumab could improve DPU disease activity.	Not serious	Not serious	Not serious	N/A	N/A	Very Low	Metz, <i>et al.</i> , 2014 ²¹ Metz, <i>et al.</i> , 2014 ³⁸ Ghazanfar, <i>et al.</i> , 2016 ³⁷ Pinto, <i>et al.</i> , 2017 ⁴² (non-RCTs)
Sulphones											
Dapsone	Subjective assessment	+	2	Two studies showed that dapsone led to clinical response and subjective improvement in DPU.	Serious	Not serious	Not serious	N/A	N/A	Very Low	Dayani, <i>et al.</i> , 1992 ³⁴ Grundman, <i>et al.</i> , 2011 ³⁵ (non-RCTs)
Sulfasalazine	Subjective assessment	+	1	One study showed that sulfasalazine led to reduction in DPU symptoms.	Not serious	N/A	Not serious	N/A	N/A	Very Low	Swerlick, <i>et al.</i> , 2015 ³⁶ (non-RCTs)
Other drugs											
Indomethacin	Provocation with dermographometer	-	1	One study showed no significant differences in size of DPU lesions between indomethacin and placebo	Not serious	N/A	Not serious	N/A	N/A	Moderate	Dover, <i>et al.</i> , 1988 ⁹ (crossover) (RCTs)
Colchicine	Provocation with dermographometer	-	1	One study showed no significant difference in size of DPU lesions between colchicine and placebo	Not serious	N/A	Not serious	N/A	N/A	Moderate	Lawlor, <i>et al.</i> , 1989 ⁶ (crossover) (RCTs)
Intravenous immunoglobulin (IVIG)	Subjective assessment	+	1	One study showed that IVIG led to clinical improvement and reduction in DPU episodes.	Not serious	N/A	Not serious	N/A	N/A	Very Low	Dawn, <i>et al.</i> , 2003 ²⁰ (non-RCTs)
Gluten-free diet	Subjective assessment	+	1	One study showed that gluten-free diet led to initial improvement of DPU lesions.	Serious	N/A	Not serious	N/A	N/A	Very Low	Bazex, <i>et al.</i> , 1994 ⁴⁰ (non-RCTs)

DPU, Delayed pressure urticaria; *N/A*, data not available in the study.

†The level of evidence of supporting study according to the GRADE system, for classification of evidence: the quality of evidence at one of four levels: high, moderate, low, and very low based on five downgrade factors: LIM (limitations), INC) inconsistency, (IND) indirectness, (IMP) imprecision and (PB) publication bias. *Imprecision was evaluated by effect size and 95% confidence interval. **Publication bias was identified by funnel plot. Given that this study is a systematic review without meta-analysis, imprecision and publication bias could not be evaluated.

#Efficacy of the study: + = study supports efficacy of treatment; - = study does not support efficacy of treatment.