

Expert Opinion

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Chronic urticaria: a comparison of management guidelines

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Introduction: Chronic urticaria is characterized by recurring episodes of spontaneous transient dermal wheals and pruritus, with or without angioedema, which can persist for ≥ 6 weeks. Chronic urticaria impairs quality of life, emphasizing the need for effective treatments. Professional societies and clinical experts have issued evidence-based recommendations for the management of chronic urticaria, including recommending the use of second-generation antihistamines as a first-line therapy.

Areas covered: A Medline search was conducted from 2000 to 2011 using the following terms, alone or in combination: 'chronic urticaria', 'management guidelines', 'consensus guidelines' and 'expert opinions'. Ten management guidelines/expert opinions met the inclusion criteria.

Expert opinion: There was a universal agreement among the articles reviewed, that low-sedating, second-generation antihistamines should be prescribed as a first-line treatment of chronic urticaria. For refractory urticaria, however, recommendations varied and included dose escalation of second-generation antihistamines and adjunctive treatments with other agents of the same class, such as sedating antihistamines or leukotriene receptor antagonists. More research into effective second-line treatments and consistent implementation of current guidelines is needed, to ensure that treatment is based on clinical evidence.

Keywords: antihistamines, chronic urticaria, expert opinion, management guidelines, second-generation, up-titration

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1. Introduction

Chronic urticaria is a skin disorder characterized by the spontaneous occurrence of widespread, transient wheals and pruritus, often accompanied by angioedema, persisting for ≥ 6 weeks [1,2]. These symptoms, typically unrelated to external physical stimuli, are primarily mediated by the release of histamine from mast cells [1,3].

The prevalence of chronic urticaria has been difficult to estimate because the diagnosis is frequently one of exclusion [2], although Greaves suggests that chronic urticaria accounts for 25% of cases of urticaria [4]. The disease is subject to recurrence and may persist for decades [5]. As many as 40% of patients who have chronic urticaria for > 6 months continue to experience urticarial wheals 10 years later [6]. Studies have shown that individuals with chronic urticaria have significantly lower physical capacity, greater bodily pain, poorer general health and reduced emotional well-being compared with patients who have respiratory allergies [6]. Moreover, the negative effects of chronic urticaria on several aspects of quality of life (QOL) are as severe as those of more serious conditions, including ischemic heart disease [7,8]. The physical and mental impairment resulting from chronic urticaria underscores the need for prompt diagnosis and initiation of optimal therapy.

The purpose of this review is to define the commonalities and differences among the various guidelines and expert opinions, to highlight areas of consensus and disagreement and to identify issues that require further evaluation and discussion.

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Article highlights.

- Management guidelines/clinical recommendations for chronic urticaria universally recommend low-sedating, second-generation antihistamines as first-line treatment.
- For refractory chronic urticaria, guidelines/clinical recommendations advocate a stepwise approach, including increased doses of second-generation agents, adjunctive therapy with a first-generation antihistamine, an additional second-generation antihistamine, or agents from other classes.
- Additional research is needed to identify the optimum second-line treatments for chronic urticaria that does not respond to low- or non-sedating second-generation antihistamines.
- More consistent implementation of current guidelines is needed to ensure that treatment is based on the available evidence.

This box summarizes key points contained in the article.

2. Methodology

The Medline database was searched for guidelines and expert opinions published between 2000 and 2011 on the diagnosis and management of chronic urticaria, using the following terms, alone or in combination: 'chronic urticaria', 'management guidelines', 'consensus guidelines' and 'expert opinions'. Ten guidelines/expert opinions were published between 1 January 2000 and 30 November 2010. The reference lists of these guidelines/expert opinions were reviewed for additional publications. No additional guidelines or expert opinions were identified from these publications or beyond 2010.

3. Clinical guidelines and expert opinions

3.1 First-line therapy

Based on extensive evidence from controlled trials, clinical guidelines universally recommend second-generation oral antihistamines as first-line monotherapy for chronic urticaria (Table 1) [3,9-16]. Published expert opinions, which do not carry the same weight as formal guidelines, offer useful advice for the application of current clinical evidence in daily practice. As with clinical guidelines, published expert opinions recommend second-generation antihistamines as the preferred first-line treatment for chronic urticaria [14-17].

3.2 Approaches to management of refractory urticaria

3.2.1 Increasing doses of second-generation antihistamines

In clinical practice, dose escalation with second-generation antihistamines has become commonplace for the management of patients with chronic urticaria who do not respond adequately to standard doses, provided potential benefits outweigh risks [9,13]. Although not indicated on the approved

labels of any second-generation antihistamine, this strategy has been recommended in some clinical guidelines and published expert opinions (Table 2) [3,9-11,13,14,18]. Updated guidelines issued in October 2009 by the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) advise that patients who have unsatisfactory responses to standard doses of second-generation antihistamines should receive doses up to four times higher than standard before alternative therapies are considered [3]. According to these guidelines, the majority of patients with refractory urticaria will benefit from uposing [3]. Evidence indicates that non-sedating second-generation antihistamines retain their favorable safety profiles at higher-than-indicated doses and that, in some cases, their efficacy increases [16]. However, opinions vary: according to one published expert opinion, increasing the dosage to more than twice the recommended level was found to be beneficial only rarely in clinical experience [14]. Recommendations for the use of high-dose, non-sedating second-generation antihistamines is not yet evidence based [9,17]. Additional clinical studies are needed to clarify the effects of such regimens in treatment-refractory chronic urticaria [3,9,17].

3.2.2 Substituting another second-generation antihistamine

Unlike the EAACI/GA²LEN/EDF/WAO recommendations, the Société Française de Dermatologie (SFD) guidelines for the management of chronic urticaria stipulate that the dose of a second-generation antihistamine should conform to that of the approved label [11]. Accordingly, patients who do not achieve complete remission after 4 – 8 weeks of treatment at the indicated dose of one second-generation antihistamine may be switched to another molecule of the same class.

3.2.3 Switching to an alternative therapy

Despite safety concerns, some guidelines and published expert opinions continue to recommend first-generation antihistamines as alternative therapy for patients with suboptimal responses to high-dose second-generation agents. The SFD guidelines advise that patients who fail to respond to a 4- to 8-week trial of one second-generation antihistamine should switch to another second-generation agent or to a first-generation antihistamine [11]. However, the panel found no information in the literature to indicate that one of these strategies is preferable to the other.

One published expert opinion advises that patients with suboptimal responses to high-dose second-generation antihistamines should be switched to a first-generation antihistamine, with the dose given at bedtime and gradually increased based on tolerance to sedation [14]. Another recommends substituting high doses of first-generation antihistamines, supplemented by H₂-antagonists and leukotriene-receptor antagonists (LTRAs), when second-generation agents are ineffective [19].

Table 1. Recommendations for first-line treatment of chronic urticaria: representative sampling of clinical guidelines and expert panel opinions.

Ref.	Recommendations
<i>Guidelines</i>	
EAACI/GA ² LEN/EDF/WAO guideline [3] BSACI guidelines [9]	Second-generation H ₁ -antihistamines should be considered first-line symptomatic treatment Sedating antihistamines should not be used for routine management as first-line agents Nonsedating H ₁ -antihistamines are the mainstay of therapy Chronic use of first-generation antihistamines should generally be avoided because of sedation and psychomotor retardation
AAITO position paper [10]	Low-sedating H ₁ -antihistamines as first-line therapy Sedating H ₁ -antihistamines if the patient is anxious and disturbed at night
SFD Consensus Conference Recommendations [11] Joint Task Force on Practice Parameters [12]	Monotherapy with a second-generation H ₁ -antihistamine is the preferred treatment These drugs enable the disease to be controlled in the majority of patients Symptomatic treatment with H ₁ -antihistamines remains the mainstay of management for most patients; sedation does not occur at recommended doses of these agents with the exception of cetirizine, which may have sedative effects in a small percentage of patients Sedation from first-generation antihistamines may reduce the discomfort of pruritus, but these agents may cause undesirable and potentially dangerous side effects
BAD therapy guidelines [13]	Nonsedating H ₁ -antihistamines are the mainstay of therapy Patients should be offered the choice of at least two nonsedating antihistamines because responses and tolerance vary among individuals
<i>Expert opinions</i>	
Khan 2008 [14] Muller 2004 [15] Kaplan 2002 [16]	Second-generation antihistamines must be considered as first-line symptomatic treatment Second-generation H ₁ -receptor antagonists should be used as first-line treatment There is general agreement that nonsedating antihistamines are the first choice for treatment

AAITO: Associazione Allergologi Immunologi Territoriali Ospedalieri; BAD: British Association of Dermatologists; BSACI: British Society for Allergy and Clinical Immunology; EAACI/GA²LEN/EDF/WAO: European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization; SFD: Société Française de Dermatologie.

3.2.4 Initiating adjunctive therapy

Some authorities continue to recommend first-generation antihistamines as adjunctive treatment when chronic urticaria does not respond to second-generation antihistamines. The practice parameters issued by the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy Asthma and Immunology) note that various combinations of first- and second-generation antihistamines have been used to treat patients whose chronic urticaria symptoms are refractory to monotherapy with the latter class of agents [12]. Guidelines developed by the British Society for Allergy and Clinical Immunology state that patients who fail to respond to high-dose nonsedating antihistamines should be given a second agent from the same class as adjunctive therapy, with a sedating antihistamine added at night if required to achieve optimal response [9]. However, continuous use of first-generation antihistamines should generally be avoided because of the risks of somnolence and psychomotor obstruction [9]. The guidelines developed by the British Association of Dermatologists note that the addition of a sedating antihistamine at night may improve sleep but will probably have little clinical effect on urticaria symptoms if the H₁-receptor is already saturated [13]. One expert opinion recommends considering nighttime dosing of sedating antihistamines not only when monotherapy with second-generation antihistamines

has failed but also as part of the first-line regimen, with a nonsedating antihistamine given during the daytime [16].

Several other adjunctive regimens have been proposed as well. The Joint Task Force guidelines state that patients whose chronic urticaria symptoms are refractory to monotherapy with second-generation H₁-antihistamines may benefit from the addition of H₂-antihistamines [12]. By contrast, the EAACI/GA²LEN/EDF/WAO guidelines hold that the use of regimens such as nonsedating H₁-antihistamines plus adjunctive H₂-antihistamines or LTRAs is based on low levels of evidence from randomized, controlled trials [1]. Data on the use of adjunctive doxepin to tricyclic antidepressants are also limited in the estimation of the EAACI/GA²LEN/EDF/WAO [1]. By contrast, the guidelines indicate that strong evidence is available to support the efficacy of cyclosporine in combination with second-generation antihistamines. The poor safety profile and high cost of cyclosporine argue against its use in chronic urticaria.

Some expert opinions recommend a trial of adjunctive therapy with an H₂-receptor antagonist, cyclosporine, doxepin, and/or an LTRA when patients with chronic urticaria do not respond adequately to first-line treatment with second-generation antihistamines, even at high doses [10,14,16,19]. Although the use of systemic corticosteroids is not usually advisable because of the risk of toxicity, tolerance issues and exacerbation of symptoms after drug withdrawal, some clinicians opt for short courses of prednisone when the primary objective is rapid control of chronic urticaria [10,16].

Table 2. Recommendations for dosing of second-generation antihistamines in patients with chronic urticaria unresponsive to standard doses.

Ref.	Recommendations
<i>Guidelines</i>	
EAACI/GA ² LEN/EDF/WAO Guideline [3]	Doses of non-sedating H ₁ -antihistamines should be increased if necessary, up to 4-fold
BSACI Guidelines [9]	Studies suggest that the majority of patients with urticaria will profit from up-dosing with antihistamines, although more research is needed in different subtypes (such as CU) It is common practice to increase the dose of a non-sedating H ₁ -antihistamine above the normal recommendation when potential benefits are considered to outweigh the risks in patients who do not achieve adequate symptom relief at standard doses A step-up treatment plan is recommended wherein the progression between steps depends on clinical severity and response; patients who do not respond adequately to initial therapy with a standard-dose non-sedating H ₁ -antihistamine should be stepped up to a higher dose before a second non-sedating antihistamine is added or alternative therapy is considered
AAITO position paper [10]	Steroid therapy; if patient reports NSAID hypersensitivity, try LTRAs Cyclosporine Other therapies include tacrolimus, cyclophosphamide, methotrexate, hydroxychloroquine, warfarin, tranexamic acid. Experience with these therapies is anecdotal or limited, and they cannot be recommended for routine use
SFD Consensus Conference Recommendations [11]	H ₁ -antihistamines remain the exclusive recommended treatment Monotherapy: substitute another second-generation antihistamine Combination therapy: prescribe a second antihistamine (first- or second-generation)
BAD Therapy Guidelines [13]	It has become common practice to increase the dose of a non-sedating H ₁ -antihistamine above the manufacturer's recommended dose for patients who do not respond, when the potential benefits are considered to outweigh any risks Adjustments to the timing of medication can be helpful to ensure that the highest drug levels are obtained when urticaria is anticipated
<i>Expert opinion</i>	
Khan 2008 [14]	It is well recognized that many patients with CU may not respond to typically recommended doses of second-generation antihistamines and higher doses may be required Higher doses do improve some patients, but increasing beyond twice the recommended dose is rarely beneficial

AAITO: Associazione Allergologi Immunologi Territoriali Ospedalieri; BAD: British Association of Dermatologists; BSACI: British Society for Allergy and Clinical Immunology; CU: Chronic urticaria; EAACI/GA²LEN/EDF/WAO: European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization; LTRAs: Leukotriene-receptor antagonists; NSAID: Nonsteroidal anti-inflammatory drug; SFD: Société Française de Dermatologie.

4. Discussion

4.1 First-line therapy

The considerable adverse impact of chronic urticaria on QOL points to the need for effective treatment [1,6,7]. Clinical guidelines and published expert opinions have attempted to identify strategies for optimizing patient response to therapy and improving overall outcomes. The consensus is that second-generation oral antihistamines are the preferred first-line therapy for chronic urticaria. This recommendation is based on a large body of data from controlled studies confirming the efficacy of these agents in treating chronic urticaria symptoms and improving QOL [2,20-47].

4.2 Management of refractory urticaria

4.2.1 Escalating doses of second-generation antihistamines

Recommendations for increasing doses of non-sedating second-generation antihistamines in patients with treatment-refractory chronic urticaria are supported by clinical trial data, although evidence remains limited, and it is not indicated on any

approved labels for second-generation antihistamines. A recent double-blind, randomized study found advantages when non-sedating second-generation antihistamines were given in doses up to four times that indicated [48]. In 80 patients with chronic urticaria, scores reflecting discomfort from symptoms as well as overall QOL showed that ~ 10% responded to 5 mg/day of either desloratadine or levocetirizine, 75% responded to 20 mg/day, and 15% remained unresponsive even at the higher dosage. The investigators concluded that most patients with chronic urticaria who do not respond to indicated doses of non-sedating second-generation antihistamines would benefit from higher doses.

The advantages of higher doses are also supported by data indicating that the therapeutic effects of second-generation antihistamines are dose dependent. For example, two randomized, double-blind, placebo-controlled studies found that pruritus scores improved and the number of wheals decreased significantly, in a linear fashion, as the dose of fexofenadine was increased in patients with chronic urticaria [40,42]. In a randomized, double-blind, three-way crossover trial involving 31 patients with cold urticaria,

symptoms improved significantly with the standard 5-mg dose of desloratadine but improved more with doses up to four times higher [49].

Trials of high-dose cetirizine, however, have yielded inconsistent results. One study enrolled 21 patients with chronic urticaria who had not responded satisfactorily to various standard doses of second-generation antihistamines [50]. Following treatment with the indicated dosage of cetirizine (10 mg/day) during the screening period, all patients received 20 mg/day for 1 – 2 weeks. The patients were then randomized to continue at the 20-mg/day dosage or were downtitrated to 10-mg/day for an additional 1 – 2 weeks. Total urticarial activity scores, as well as individual scores for wheal, itch and symptom duration, showed additional improvement in patients who remained at the high dosage but worsened in those who returned to the conventional dose; these differences were significant ($p < 0.01$). These results conflicted with data from an open-label assessment of 22 patients with chronic urticaria who had not responded satisfactorily to standard treatment with antihistamines [51]. The patients received cetirizine 10 mg/day for 1 week, followed by 30 mg/day for a second week. Only one patient (5%) reported marked benefit with the increased dose, whereas the remaining 21 patients (95%) had no improvement; 13 patients (59%) experienced fatigue and somnolence. The nonresponders required more aggressive therapy with corticosteroids, cyclosporine or other immunosuppressants.

Clinical trials have shown that up dosing of most second-generation antihistamines is safe. Treatment with desloratadine over a dose range of 5 mg/day (the standard adult dosage) to 20 mg/day was not associated with a rising incidence of adverse events [49]. In a double-blind, randomized, crossover study of 20 healthy volunteers, Japanese investigators found that fexofenadine 120 mg/day (twice the recommended dosage at the time of the study) did not cause somnolence, impairment of performance on psychometric tasks or increased subjective sleepiness scores [52]. By contrast, the administration of cetirizine at 20 mg/day resulted in significant detriments from baseline in various psychometric tasks, as well as significant impairment when compared with fexofenadine at twice the recommended dosage. Occupancy of the H_1 -receptor in the cortex was negligible with fexofenadine (-0.1%) but was moderately high with cetirizine (26%). Another double-blind, randomized, crossover study showed the effects of fexofenadine 360 mg/day (twice the recommended dosage) on psychomotor performance and cognitive function did not differ from those of placebo in 14 healthy volunteers [53].

4.2.2 Combination regimens

Additional treatment strategies have been proposed for patients who do not respond to second-generation antihistamines, even at high doses. Adding a sedating antihistamine or combining two non-sedating antihistamines is likely to be ineffective, as increased plasma concentrations of

H_1 -antagonists would force the compounds to compete for the same receptors [54]. Nevertheless, some authorities continue to recommend the addition of first-generation antihistamines for patients who have suboptimal responses to standard doses of second-generation antihistamines, particularly to alleviate symptoms that interfere with sleep [13,16]. Studies have confirmed that first-generation antihistamines are associated with increased risks of occupational injuries, impaired driving performance, fatigue and diminished cognitive abilities (attention, working memory, vigilance, speed), as well as reduced school performance among children [55,56]. These adverse effects can occur even when the medication is taken the night before [55]. Combining non-sedating antihistamines with other non-sedating or sedating compounds can also be associated with a risk of drug–drug interactions and related adverse events [54]. A further consideration is the fact that patients are frequently unaware of the degree to which their performance is impaired after taking sedating antihistamines, so they are unlikely to use appropriate caution when performing potentially dangerous tasks, such as driving a car or operating heavy machinery [55]. Research has also shown that warning labels regarding sedation that appear on packages for first-generation antihistamines are not generally taken seriously by patients [55].

The combination of H_1 - and H_2 -antihistamines has been widely used and studied in patients with refractory chronic urticaria [54,57,58]. In older randomized, placebo-controlled trials involving patients with chronic urticaria, significant benefits were achieved through the addition of the H_2 -antihistamine cimetidine to first-generation H_1 -antihistamines (chlorpheniramine, diphenhydramine, or hydroxyzine) [57-59]. A subsequent pharmacokinetic assessment in 16 chronic urticaria patients unresponsive to H_1 -antihistamine monotherapy found that coadministration of cimetidine significantly increased serum concentrations of hydroxyzine and improved suppression of wheal and flare [60]. However, such was not the case when the second-generation agent cetirizine was given in combination with cimetidine; the pharmacokinetics of cetirizine did not change significantly, and wheal and flare suppression was not enhanced. The investigators concluded that there is no therapeutic rationale for treating chronic urticaria with cetirizine plus cimetidine. The prevailing view is that increased efficacy is more likely to occur when H_2 -antihistamines are combined with H_1 -antihistamines that share a common metabolic pathway in the liver (such as chlorpheniramine or hydroxyzine) as opposed to those that do not (such as cimetidine) [54]. The combined effects of H_1 - and H_2 -antihistamines may be due to interactions at the level of cytochrome P3A4 or other isoenzyme families (resulting in mutual increases in the area under the plasma drug concentration-time curve) rather than to a true synergistic effect.

Additional perspectives emerged from a more recent randomized study of 120 patients newly diagnosed with chronic urticaria [61]. Urticaria activity scores were improved significantly among those receiving therapy with

the H₁-antihistamine hydroxyzine plus the H₂-antihistamine famotidine. The relative response was greater with this regimen (63.3%) than with the combination of sedating and nonsedating H₁-antihistamines (hydroxyzine plus cimetidine, 23.3%) or a sedating H₁-antihistamine and LTRA (hydroxyzine plus montelukast, 53.3%).

Other studies have also examined the effects of combining nonsedating second-generation antihistamines and LTRAs (montelukast or zafirlukast) in chronic urticaria patients, with mixed results [62-65]. The overall findings seem to indicate that the addition of an LTRA may have some benefit in chronic urticaria refractory to monotherapy with an H₁-antihistamine but only in certain subsets of patients: those with autoimmune chronic urticaria (confirmed by positive autologous serum skin tests; ASSTs), those with food additive hypersensitivity and those who experience flares due to aspirin and other NSAIDs [63,64,66]. Even so, the likelihood of a good response is unpredictable [13].

A short course of corticosteroids may be appropriate as an adjunct to a second-generation antihistamine to shorten the duration of flares in patients with severe chronic urticaria [13,66]. However, these agents are not recommended for long-term use because of unavoidable and severe adverse effects [13].

A study involving 65 patients receiving desloratadine monotherapy for chronic urticaria found that the addition of dapsone significantly reduced symptoms [67]. However, more research is needed to explore the potential role of dapsone in chronic urticaria.

4.2.3 Alternative therapies

There are very few data to support strong recommendations for the use of alternative agents, such as corticosteroids and other immunosuppressants, dapsone, hydroxychloroquine, methotrexate, omalizumab, or sulfasalazine, as monotherapy or adjunctive therapy for refractory chronic urticaria. Evidence for their efficacy comes largely from small or open-label studies or from case reports. Thus, large, well-designed, controlled trials should be conducted to determine what place these interventions have in the treatment of chronic urticaria unresponsive to first- and second-line treatment.

Corticosteroids are strongly recommended for acute spontaneous urticaria by the EAACI guidelines, although based on weak evidence [3]. However, one large open-label study of 750 adult patients with refractory chronic urticaria found that a single short course of prednisone provided symptom remission in 47% of subjects; another 9% responded to a second course of the corticosteroid. Onset of action was rapid, beginning as early as the day after first dose [68]. Adverse events associated with corticosteroids limit their use in chronic disease, however [13].

Findings from three small, open-label studies point to the monoclonal antibody omalizumab as effective in the treatment of chronic urticaria refractory to antihistamines [69-71]. In an exploratory study, Kaplan *et al.* [71] found statistically

significant ($p = 0.0002$) decreases from baseline in mean urticarial activity scores at 4 weeks and continued to end of study in 12 patients with persistent symptoms of chronic urticaria for at least 6 weeks despite maximal antihistamine treatment. A significant ($p < 0.004$) reduction in hydroxyzine rescue medication was also observed during the final 4 weeks of the study. These results are supported by several case study reports [72-74]. The most common adverse events reported with omalizumab include arthralgia, general pain, arm pain, leg pain, fatigue, dizziness, fracture, pruritus, dermatitis and earache. Malignancies have also been observed in clinical studies.

Cyclosporine A has also been investigated in chronic urticaria. In two small studies of patients with chronic urticaria unresponsive to standard doses of nonsedating second-generation antihistamines, significant benefit was achieved by switching to cyclosporine 4 or 5 mg/kg/day [75,76]. All patients in these trials had positive ASSTs. Some patients with chronic urticaria and negative ASSTs have also been observed to respond to cyclosporine, but beneficial outcomes are less predictable [75]. Symptom improvement was also observed in a trial of cyclosporine in 27 patients with idiopathic chronic urticaria (CIU) compared with 24 healthy controls [77]. Reduction in urticaria activity score was significant in all patients ($p < 0.005$); 19 patients (70.4%) achieved complete remission by the end of the study. Serum concentrations of IL-2, IL-5 and TNF- α were significantly ($p = 0.001$) reduced in the treated subjects. In a double-blind, randomized, three-arm study, cyclosporine added to cetirizine resulted in fewer relapses in the treatment group receiving cyclosporine for 16 weeks compared with those in the 8-week and placebo groups. Symptom scores were significantly improved in both treatment groups compared with placebo ($p \leq 0.05$) [78]. Current guidelines do not recommend cyclosporine except for patients with severe disease refractory to any dose of antihistamine because of safety concerns [3].

The sulfone derivative dapsone has antibacterial and anti-inflammatory properties that may help resolve urticarial symptoms. In three small, 12-week, open-label studies of dapsone 25 – 100 mg/day for up to 3 months [67,79,80], most patients reported complete or partial symptom improvement. Relapse occurred in some patients who discontinued dapsone; symptoms resolved once dapsone was reinstated in most. Although well tolerated in these studies, dapsone has been associated with dose-related anemia, peripheral neuropathy, rash and gastrointestinal complaints [81].

Little evidence is available to support the use of LTRA monotherapy as an alternative to H₁-antihistamine monotherapy in chronic urticaria [62]. Some placebo-controlled trials of montelukast have reported benefits in chronic urticaria patients, whereas other studies of montelukast or zafirlukast have found no significant therapeutic effects [82-85].

Methotrexate, an antimetabolite with possible immunosuppressive properties, is another agent with scant evidence to back its efficacy in chronic urticaria. Research indicates that methotrexate may contribute to chronic urticaria

improvement by inhibiting or altering cytokine and chemokine activity [86]. Results from one study show that methotrexate may provide a steroid-sparing regimen for patients with antihistamine-resistant chronic urticaria responsive to corticosteroids [86]. Use of methotrexate is associated with alopecia, gastrointestinal complaints, hepatotoxicity, infection, marrow suppression, rash and stomatitis [87].

In a small, open-label, uncontrolled trial, nine chronic urticaria patients unsuccessfully treated with antihistamines and/or corticosteroids reported significantly reduced pruritus and wheal scores ($p < 0.002$ and $p < 0.004$, respectively) after 6 weeks of mycophenolate 1000 mg b.i.d. At 12 weeks, significant ($p < 0.001$) reduction in urticarial activity score was observed [88]. Mycophenolate was well tolerated. Gastrointestinal complaints and, rarely, leukopenia, anemia and dose-dependent immune suppression-related infections have been reported with mycophenolate use [81].

One case study of cyclophosphamide (i.v. 500 mg increasing to 1500 mg/month) in one subject with CIU of 20 years' duration unresponsive to antihistamines but controlled on prednisone 35 mg/day has been reported [89]. At 7 months, the subject was in complete remission, allowing discontinuation of high-dose prednisone. Cyclophosphamide was well tolerated in this subject. Adverse effects associated with cyclophosphamide include gastrointestinal complaints, malaise, alopecia, marrow suppression and stomatitis [87]. Rare cases of rash, cystitis, delayed neoplasia, immune deficiency and infertility have also been reported. Similar results have been observed in other small open-label studies or case reports in sirolimus, tacrolimus, hydroxychloroquine and sulfasalazine [90-95].

5. Conclusion

Second-generation antihistamines are universally recommended as first-line therapy for chronic urticaria, according to official guidelines and published expert opinions. Stepwise management of chronic urticaria is advised in patients who have suboptimal responses to indicated doses of second-generation antihistamines. Although there is little evidence to support the recommendation, and it is not indicated in approved labels, a trial of doses up to four times the standard levels of second-generation antihistamines is warranted before switching to another drug in the same therapeutic class or using an adjunctive therapy. Treatment of refractory chronic urticaria with higher doses of nonsedating second-generation antihistamines is generally more efficacious than treatment at standard doses, with no increase in adverse events. Evidence is lacking at present on the effectiveness of alternative agents as monotherapy for chronic urticaria. There remain many unanswered questions regarding the efficacy and safety of these alternative therapies, particularly treatment of refractory chronic urticaria with higher-than-standard doses of second-generation antihistamines, and more research through well-designed controlled trials should be conducted. Also, even as research continues to explore possible new regimens

for chronic urticaria, more consistent implementation of current guidelines is needed to ensure that treatment is based on the available evidence.

6. Expert opinion

Chronic urticaria is a prevalent and debilitating disease that impairs QOL by disrupting sleep and interfering with work productivity and social activities. The goal of treatment is not only to provide symptom relief but also to ensure that treatment does not add to chronic urticaria's considerable QOL impairment. Although professional societies and clinical experts have issued recommendations for the diagnosis and management of chronic urticaria, treatment of chronic urticaria in some patients remains suboptimal for several reasons.

First, guideline recommendations may be based on a wealth of clinical evidence, as in the case of the recommendation of second-generation antihistamines as first-line treatment for chronic urticaria [2,20-47], or largely anecdotal, such as in the nonindicated recommendation of increased dosing of second-generation agents when chronic urticaria does not respond adequately to indicated doses. Formal guidelines and opinions also vary by specialty and by geographic region.

Second, implementation of guidelines by physicians who treat chronic urticaria is inconsistent. A cross-sectional, multicenter study involving 695 patients (168 treated by allergists, 473 by dermatologists and 54 by physicians of unknown specialties) determined that nonexperts found it difficult to differentiate between chronic urticaria and various types of physical urticaria [96]. Moreover, although second-generation antihistamines (the recommended first-line therapy for chronic urticaria) were the most commonly used treatment, clinicians frequently prescribed sedating first-generation antihistamines as monotherapy or adjunctive therapy, perhaps because of a general perception that patients with chronic urticaria require a sedating drug to treat their urticaria and the accompanying anxiety. This therapeutic approach may have the opposite effect, however, undermining control of urticaria and reducing patient satisfaction with treatment.

Finally, patient adherence to chronic urticaria therapy is typically poor. In a survey of 321 patients with chronic urticaria, approximately half were receptive to taking prescription medications, but only two-thirds who received prescriptions actually took their medication [97]. Of every five patients, two reported that their physician had never discussed their emotional well-being, which compromised patient satisfaction with treatment and trust in the clinician. These results indicate that clinicians who fail to address patients' emotional responses to chronic urticaria miss opportunities to identify potential emotional problems and help the patient manage the impact of chronic urticaria on daily life.

These challenges to effective chronic urticaria management underscore the need for physicians to take a proactive approach that incorporates reassurance, attention to QOL and monitoring of satisfaction with treatment. In cases that

prove refractory to second-generation antihistamines, the best strategy at present seems to be dose intensification of the initial drug. However, it must be stressed that, in the absence of strong clinical data, it remains unclear how long higher doses of second-generation H₁-antihistamines should be continued. Moreover, further evaluation of the safety of long-term treatment with higher doses of H₁-antihistamines needs to be assessed. In the absence of definitive data on a best second-line option, physicians will need to bear in mind patient-centered variables that may argue against adoption of a combination regimen. Polytherapy, in addition to raising the risk of adverse effects, may be associated with the inconveniences of multiple dosing times and higher cost, thereby undermining compliance.

Given the continued need for more effective treatment of refractory urticaria, more research on potential combination regimens is needed. The adverse effects of first-generation antihistamines, in particular somnolence, argue against more clinical trials on the use of first- and second-generation antihistamines together. From a mechanistic standpoint, it has been pointed out that multiple H₁-antihistamines will simply compete for the same histamine receptors. Accordingly, clinical research seems warranted on agents with other pharmacologic mechanisms of action, such as H₂-antihistamines and LTRAs.

Such studies may also refine our understanding of which patient subsets may benefit most from a given regimen.

Taken together, these observations speak to the need for physicians to become more aware of the adverse impact of chronic urticaria on QOL, for compliance with current treatment guidelines to optimize outcomes, and for additional well-designed studies that will help identify the optimum second-line treatment for chronic urticaria that does not respond to standard doses of nonsedating second-generation antihistamines. In view of the fact that a high proportion (~ 25%) of urticaria patients may have chronic urticaria, these priorities must assume greater importance in dermatologic practice.

Declaration of interest

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