

Advances in the treatment of chronic urticaria

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The standard pharmacologic therapy for chronic urticaria (CU) depends on the use of medications such as type 1 antihistamines, which have been used for many years. Many newer medications that are useful in treating allergic rhinitis and asthma have not been studied extensively in patients with urticaria. A number of small but promising studies have found potential benefit from a variety of anti-inflammatory medications that are less often used but well understood. For some unusual patients, cutaneous sensitizers or ingestants are identified, and simple avoidance is sufficient.

Urticaria is a heterogeneous condition. The term “urticaria” describes the cutaneous symptoms and signs that a patient experiences. There are a number of potential causes of urticaria, and the severity and clinical pattern can vary considerably from patient to patient. For these reasons, the treatment regimen needs to be individualized.

This article discusses the established therapies for CU and the experimental evidence for the use of nonstandard and relatively unknown therapies. New agents that are under development for the treatment of allergic diseases are mentioned because of their potential for use in the treatment of CU.

Avoidance measures

As with other allergic conditions, if a specific trigger of urticaria can be identified, optimal treatment would involve the avoidance of that specific trigger. Examples include physical stimuli, specific foods, medications, and topical sensitizers. In the case of the physical urticarias (eg, cold-induced urticaria, solar urticaria, exercise-induced urticaria), avoidance of the specific physical agent would be expected to prevent recurrences of urticaria.

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Removal and reintroduction of foods in an open fashion commonly is used to establish causality. This practice is often unhelpful for patients with CU, however. If this approach is done, patients should attempt to reintroduce suspected foods in an organized fashion to avoid lifetime use of an unnecessarily restricted diet. In patients with a history of significant angioedema or anaphylaxis, reintroduction should be done under the direct supervision of a skilled physician. In select cases, a double-blind, placebo-controlled food challenge may be indicated.

Some cases of urticaria may be caused exclusively by nonallergic triggers (some of which may cause direct release of histamine from skin mast cells). Examples of this type of trigger include use of aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs) [1,2], and opiates. If one of these agents is found to be a triggering factor, avoidance is prudent.

Thirty percent to 50% of patients with CU are believed to have autoantibodies to the high-affinity receptor for IgE (FcεRI) and are considered to have autoimmune CU. An additional 30% to 50% of cases of CU have no identifiable cause. Therefore, eighty percent to 90% of patients do not have a physical trigger-, food-, topical sensitizer-, or drug-induced condition. These patients traditionally are referred to as having chronic idiopathic urticaria. Some patients with CU might describe a number of factors that do not seem to be exclusive in causing urticaria but seem to lead to an exacerbation or worsening of the urticaria. Examples might include a physical trigger, such as prolonged pressure to the skin; a nonspecific releaser of histamine (eg, an NSAID [2,3]); or psychosocial stress. In this instance, avoidance of this specific exacerbating factor might be of some benefit, although little experimental evidence supports such a recommendation. If a patient has no clearly identifiable physical, cutaneous, or ingestant trigger, avoidance measures are unlikely to be of benefit.

Treatment of underlying diseases

Urticaria rarely may be a manifestation of an underlying disease (see article by Dibern and Dreskin elsewhere this issue), and in these cases, treatment of the underlying condition may be warranted. Little experimental evidence shows that treatment of underlying conditions leads to a clinical improvement of urticaria. The best example of a systemic condition that commonly is associated with CU is Hashimoto's thyroiditis [4–7]. Treatment with thyroxine has been reported to alleviate the urticaria. This topic is discussed later in this article and more extensively by Schocket and Rumbyrt in another article in this issue. Other underlying medical conditions that have been reported to be associated with urticaria rarely are seen as a cause of urticaria, and the evidence supporting these associations is less substantiated. Examples of other conditions include cryoglobulinemia [8] and endocrine tumors [9]. A few reports have suggested that *Helicobacter pylori* might be associated with urticaria in some patients [10–13], but the data is not strongly supported.

Pharmacotherapy

H₁ antagonists

H₁ receptor antagonists (antihistamines) are considered the first line of treatment for acute urticaria and CU. Histamine is known to be an important mediator in urticaria [14,15]. The older, first-generation H₁ antagonists are effective in reducing the symptoms and number of lesions of urticaria. Higher doses often are more effective than lower doses, but may lead to side effects such as sedation, cognitive impairment, dry mouth, and urinary retention. Because of these side effects, chronic or around-the-clock use may not be desirable. Some individuals may develop a tolerance to these side effects, but this occurrence is highly variable among patients. The newer, second-generation H₁ antagonists are generally less sedating. Use of some of these drugs (eg, loratadine, fexofenadine, desloratadine) does not result in increased rate of sedation (compared with placebo) at the recommended doses, and such drugs are considered to be

Table 1
Commonly used first-generation H₁ antagonists

Drug	Recommended adult dosage	Recommended pediatric dosage	Comments
Chlorpheniramine (Chlor-Trimeton)	4 mg PO every 4–6 h 10–20 mg per dose IV/IM/SC; not to exceed 40 mg/d	2–6 y: 1 mg PO every 4–6 h not to exceed 4 mg/d 6–12 y: 2 mg PO every 4–6 h; not to exceed 12 mg/d	Pregnancy category B
Cyproheptadine (Periactin)	2–4 mg PO three times daily	2–6 y: 2 mg two or three times daily 7–14 y: 2–4 mg two or three times daily	A drug of choice for primary acquired cold urticaria
Diphenhydramine (Benadryl)	25–50 mg every 4–6 h PO/IV/IM	5 mg/kg/d PO/IV/IM divided three or four times daily; not to exceed 300 mg/d	
Doxepin (Sinequan)	10–150 mg/d PO at bedtime or divided two or three times daily	> 12 y: 10–50 mg/d PO at bedtime or divided two or three times daily and can increase gradually to 100 mg/d	Tricyclic antidepressant Begin with a low dose (10–25 mg at bedtime) first
Hydroxyzine (Atarax, Vistaril)	10–100 mg every 6–8 h PO/IM	0.6 mg/kg/dose PO every 6 h 0.5–1 mg/kg/dose IM every 4–6 h	A drug of choice for primary acquired cold urticaria

Abbreviations: IM, intramuscularly; IV, intravenously; PO, orally; SC, subcutaneously.

nonsedating. Others drugs (eg, cetirizine) can produce sedation in a minority of patients [16–18], although not to the same degree as seen with first-generation agents [16,17]; these drugs have been labeled by some clinicians as minimally sedating. Many clinicians recommend the use of second-generation agents for chronic or around-the-clock treatment and first-generation agents for severe cases or acute exacerbations. Some clinicians also advocate the use of a second-generation agent during the day, with a dose of a first-generation agent at night (to minimize sedation during the day). Some tricyclic antidepressants, such as doxepin, have potent H₁ and H₂ antihistaminic activity and can be helpful when used as antihistamines [19,20], although they often cause considerable sedation and anticholinergic side effects, such as dry mouth [20]. Table 1 shows some of the commonly used first-generation H₁ antagonists. Table 2 shows the second-generation agents that are on the market in the United States and shows the Food and Drug Administration (FDA)-approved doses. At these doses, second-generation H₁ blockers have been shown to be superior to placebo in multiple clinical trials, although the degree of efficacy is modest. Many clinicians use second-generation antihistamines in doses that are higher than the FDA-approved dose, although no controlled trials demonstrate significantly increased efficacy with use of higher doses. Higher doses of the second-generation agents may lead to increased side effects, although this finding has also not been well studied. Mizolastine, a new second-generation agent that is available in Europe (but that is not FDA approved in the United States) has been found to be effective for the

Table 2

Commonly used second-generation H₁ antagonists

Drug	Recommended adult dosage	Recommended pediatric dosage	Comments
Cetirizine (Zyrtec)	5–10 mg PO once per day	6–12 mo: 2.5 mg PO once per day 12–23 mo: 2.5 mg PO once per day to two times daily 2–5 y: 2.5–5 mg PO once per day or 2.5 mg PO two times daily >6 y: 5–10 mg PO once per day	May cause sedation in approximately 10%–14% of patients Pregnancy category B
Desloratadine (Clarinex)	5 mg PO once per day	Not established for children younger than 12 y	Rate of sedation similar to that with placebo A metabolite of loratadine
Fexofenadine (Allegra)	60 mg PO two times daily	<6 y: not established 6–11 y: 30 mg PO two times daily	Rate of sedation similar to that with placebo
Loratadine (Claritin)	10 mg PO once per day	2–5 y: 5 mg PO once per day >6 y: administer as in adults	Rate of sedation similar to that with placebo Pregnancy category B

Abbreviation: PO, orally.

treatment of chronic idiopathic urticaria [21] and primary acquired cold urticaria [22]. Ketotifen, another agent that is not FDA approved, has antihistamine- and mast cell-stabilizing properties and has been found to have efficacy in the treatment of CU [23,24], cholinergic urticaria [25], and physical urticarias [26–28].

H₂ antagonists

H₂ receptors are found in large numbers in the stomach. For this reason, H₂ antagonists (eg, ranitidine, cimetidine) primarily are used to inhibit gastric acid secretion; however, H₂ receptors also are present in the skin and may contribute to the cutaneous effects of histamine. The addition of an H₂ antagonist to an H₁ antagonist in treating CU can be more effective than an H₁ antagonist alone, as confirmed in small trials [29–31]. One of these studies found that 40% to 50% of patients had statistically significant improvement when cimetidine was added to hydroxyzine [29]. Other small trials have not seen this additive effect [32]. For some patients who experience this synergistic effect between certain H₁ and H₂ antagonists, the synergism may be caused by a pharmacokinetic effect, with the H₂ blocker leading to increased blood levels of the H₁ blocker [33]; this finding warrants further study. For dermographism, a combination of chlorpheniramine and cimetidine was found to be superior to either agent alone in a small trial [34].

Corticosteroids

In some cases of urticaria, antihistamines may not be adequate. In this setting, systemic corticosteroids are usually effective. Urticarial vasculitis, which is believed by many investigators to be a severe variant of CU, often requires the use of high-dose steroids to achieve control.

Severe episodes of acute urticaria often do not respond to antihistamines alone, and a short course of oral steroids (with or without a taper) may be effective. Standard dosages (0.5–1.0 mg/kg/d) should be used and can be titrated to achieve the desired response. In cases of CU that have not responded to H₁ antagonists (even in high doses), the use of long-term systemic corticosteroids can be considered. Although there are no large-scale, double-blind, placebo-controlled trials of the long-term use of corticosteroids in CU [35], clinical experience suggests that these drugs are efficacious in most patients, if an adequate dose is used. The likelihood of corticosteroid-induced side effects increases with longer periods of treatment, and patients should be advised of this possibility so that the risks and potential benefits can be considered carefully. The most-effective, lowest dose should be used, and doses as low as 5 mg of prednisone (or equivalent) every day or every other day may be effective.

Adrenergic agents

The use of epinephrine in urticaria should be considered only in acute cases that are accompanied by life-threatening features, including signs of anaphylaxis

or respiratory tract angioedema. Ephedrine, which has been shown to be effective when used as part of a prophylactic regimen to prevent anaphylactoid reactions in patients who are sensitive to radiographic contrast media [36], is used by some clinicians to help control the induration associated with urticaria, but no good experimental evidence supports this practice. There are conflicting reports of the usefulness of terbutaline. In vitro, it may have some effect in suppressing the wheal induced by intradermal injection of an allergen [37]. Some reports have suggested clinical efficacy [38], particularly in cold urticaria [39], whereas other studies have not found any significant clinical benefit [37,40]. Data are scarce, and large-scale, well-controlled trials have not been done. Given the high rate of side effects with these adrenergic agents, the therapeutic benefit–risk ratio for chronic use is unlikely to be favorable in most patients.

Antileukotriene agents

Preclinical evidence suggests that the leukotriene receptor antagonists (LTRAs) and leukotriene synthesis inhibitors may have some role in the treatment of urticaria. Leukotriene C₄ (LTC₄) and leukotriene D₄ (LTD₄) are believed to have roles as mediators in urticaria [41]. Studies have shown that the intradermal injection of LTC₄, LTD₄, and leukotriene E₄ produces a wheal-and-flare reaction in normal subjects [42,43] and in patients with chronic idiopathic urticaria [43]. The sera from some patients with positive autologous serum skin tests have been shown to cause histamine release and de novo production of sulfidoleukotrienes in vitro [44]. Simons et al found that montelukast decreased the cutaneous response to intradermally injected LTD₄, although montelukast was no more effective than placebo in decreasing the early and late cutaneous response to intradermally injected histamine or allergen [45].

Case reports and small clinical studies have suggested that the antileukotriene agents may have efficacy in the treatment of urticaria, but there have been no published large-scale, blinded, placebo-controlled trials, and none of the agents that are available in the United States are FDA approved for treatment of urticaria. Nettis et al reported that montelukast was more efficacious than fexofenadine for the treatment of CU, although montelukast was not compared with placebo [46]. They also reported that the autologous skin test became negative with montelukast treatment in six of nine patients who had a positive autologous skin test at the beginning of the study. Ellis described one patient who improved with zileuton, a 5-lipoxygenase inhibitor, and another patient who improved with zafirlukast and zileuton treatment [47]. The efficacy in this second patient was confirmed with a double-blind, placebo-controlled evaluation. Spector and Tan reported one patient who improved with zafirlukast treatment and a second patient who failed zafirlukast therapy but improved with zileuton [48]. Both patients were administered the agents in an open-label fashion. Asero described a patient whose CU was triggered by NSAID use and who improved with an open-label trial of montelukast and zafirlukast [49]. In an open-label, uncontrolled study, Asero et al reported that 6 of 11 patients with severe,

unremitting, steroid-dependent urticaria improved with montelukast or zafirlukast treatment [50]. Bensch and Borish reported that 10 of 18 patients with CU benefited from the open-label addition of a leukotriene modifier to their treatment regimens [51]. Nettis et al found that the combination of montelukast plus loratadine was significantly more effective than loratadine alone in preventing delayed pressure urticaria [52].

There are few published reports of blinded, placebo-controlled trials of LTRAs in CU. In a double-blind, placebo-controlled, cross-over study involving 52 patients with CU, Reimers et al found that zafirlukast was no more effective than placebo [53]. Erbagci found that montelukast was significantly more effective than placebo in a single-blind, crossover trial in 30 patients with refractory chronic idiopathic urticaria (CIU) [54]. Nine of 11 patients who initially had a positive response to intradermal injection of autologous serum had a negative test after treatment with montelukast. Patients with aspirin-sensitive urticaria had good results with montelukast in this trial.

Although there have been some promising results with LTRAs in case reports and small trials, large-scale, double-blind, placebo-controlled trials are needed to confirm whether there is a significant role for LTRAs in the treatment of urticaria. Similarly, there have been no large-scale trials with the 5-lipoxygenase inhibitor zileuton, although its use would likely be limited because of the risk for hepatotoxicity.

Thyroxine

As discussed in an article by Schocket and Rumbyrt, substantial evidence shows that CU is associated with thyroid autoimmunity; however, the pathophysiologic mechanism that may connect these two entities is not understood. As many as 12% to 14% of patients with CU have circulating thyroid autoantibodies, which is considerably higher than the incidence of 5% to 6% seen in the normal population [4,5,7]. Most of these patients are female, and many have angioedema and urticaria. Although some of these patients have clear evidence of Hashimoto's thyroiditis, mandating treatment with thyroid hormone, many are euthyroid with normal thyroid-stimulating hormone levels. Because clinical experience has shown that treatment of Hashimoto's thyroiditis with thyroxine seems to lead to amelioration of CU in some patients, there have been a number of attempts to use thyroxine to treat euthyroid patients with CU and antithyroid antibodies. The results have been variable. Leznoff et al treated seven patients who had thyroid autoantibodies but were euthyroid, with 0.2 mg/d of levothyroxine in an open-label, uncontrolled manner [5]. Five patients showed improvement of their urticaria, but this finding generally was not seen until 2 months after beginning therapy. In a later study, Leznoff et al treated 46 patients with CU and thyroid autoimmunity (some of whom were euthyroid and others who were hypothyroid) with levothyroxine, but only eight patients improved within 1 month [4]. Two of these patients who improved initially had a reappearance of urticaria despite continuation of levothyroxine; however, four

patients who improved, who had high thyroid autoantibody levels, had repeated remissions each time levothyroxine was started and repeated relapses when treatment was stopped. Rumbly et al had a better rate of success [6]: All seven euthyroid patients with CU and elevated levels of antithyroid antibodies reported resolution of symptoms within 4 weeks of starting thyroxine. Five of the seven patients had a relapse of symptoms after discontinuing thyroxine and responded again when the medication was restarted. There was no correlation between clinical response and change in antithyroid antibody levels, suggesting that the antithyroid antibodies themselves were not pathogenic. One patient in this study underwent a double-blind trial with thyroxine and placebo, in which the response to thyroxine was confirmed.

These findings suggest that some patients with CU and thyroid autoimmunity may improve with thyroxine treatment, whereas others may fail the therapy. In patients who improve, the mechanism of action is not clear. Hyperthyroid patients have no difference in response to histamine, codeine, and compound 48/80 compared with controls [55], suggesting that thyroxine itself probably does not have direct effects on mast cell release or cutaneous response to histamine. Larger double-blind, placebo-controlled trials are needed to clarify which patients, if any, respond to thyroxine.

Cyclooxygenase 2 inhibitors

As discussed previously, aspirin and other nonselective cyclooxygenase (COX) inhibitors (traditional NSAIDs) exacerbate urticaria in some patients [1,2] and usually are not used as therapy for urticaria. An exception is indomethacin, which has been used for urticarial vasculitis [56]. The exact mechanism whereby the NSAIDs may exacerbate urticaria is not known. Traditional NSAIDs inhibit COX-2 and COX-1. COX-2 has a major role in allergic diseases by synthesizing prostaglandin D₂. COX-1 is involved in the synthesis of prostaglandin E₂ (PGE₂), which is believed to be able to down-regulate the synthesis of LTC₄ [57]. PGE₂ and COX-1 may be protective in cutaneous allergic diseases such as CU. Because traditional NSAIDs inhibit both COX enzymes, any beneficial effects of the inhibition of COX-2 in patients with urticaria may be counteracted by the inhibition of COX-1.

Because the newer COX-2 inhibitors lead to the inhibition of COX-2 with minimal inhibition of COX-1, one can hypothesize that they may be helpful in treating cutaneous inflammatory diseases without the risk for exacerbating the disease. Growing evidence shows that rofecoxib generally is well tolerated in patients with a history of NSAID-induced cutaneous reactions [58–60], although rare reactions still may occur. Other COX-2 inhibitors, such as nimesulide, meloxicam, and celecoxib, which are less selective for COX-2, may not be as well tolerated and have been reported to cause a higher rate of reactions [61]. There are only scarce reports of clinical trials of these agents. Anand et al added rofecoxib to the existing regimens of eight patients with refractory CIU in an open-label fashion [62]. Five patients had complete resolution of hives within

5 to 7 days after starting rofecoxib and were able to discontinue steroids. The drug generally was well tolerated, but one patient developed lower-extremity edema and an increase in serum creatinine level that were believed to be related to rofecoxib treatment. In another small trial involving 10 patients, the open-label addition of rofecoxib to desloratadine was found to be statistically more effective than desloratadine alone [63]. More studies are needed to confirm the efficacy of these agents in CU.

Calcium-channel blockers

Limited evidence shows that the calcium-channel blocker, nifedipine, at dosages of 10 mg twice daily to 20 mg three times daily and when used in combination with an H₁ antagonist, may have some added benefit in patients who have not responded to H₁ antagonists alone [64]. These agents rarely are used in clinical practice, however, perhaps because the clinical benefit is limited and side effects, such as edema, can occur.

Warfarin

A few case reports and one limited trial report on the use of warfarin in CU. Parslew et al [65] found that six of eight patients treated in an open-label fashion responded, with dramatic responses in three patients. These three patients underwent a double-blind, placebo-controlled crossover study, which confirmed the response to warfarin. The mechanism of action responsible for the response in these patients is not known.

Other immunomodulatory and anti-inflammatory agents

Cyclosporine

A few studies indicate that oral cyclosporine can be efficacious in severe cases of urticaria. An open-label, uncontrolled trial of high-dose (6 mg/kg) cyclosporine in three patients with severe CU led to temporary but complete relief of the urticaria in all of the patients, who also experienced significant transient side effects [66]. A reduced dose of 3 mg/kg did not prevent the side effects and did not provide complete relief to the degree seen with the 6-mg/kg dose. A separate open-label trial of 12 weeks of cyclosporine therapy (with a control group that received no treatment) resulted in full remission for 13 of 19 treated patients [67]. The patients initially received a 3-mg/kg dose, which was tapered progressively over the study period. No severe side effects were reported. The autologous serum skin test became negative in five of eight treated patients who initially had a positive test. A later randomized, placebo-controlled trial of 4-mg/kg cyclosporine treatment administered over 4 weeks resulted in a significant response in 8 of 19 treated patients [68]. Drug-related side effects were reported but did not cause withdrawal from the study. A significant reduction of in vitro histamine-

releasing activity and reduction in reaction size of the autologous serum skin test was seen after cyclosporine treatment.

Plasmapheresis

A trial of plasmapheresis in eight patients with severe autoimmune (positive autologous serum skin test) CU led to variable response in six patients [69]. A decrease in the size of the skin test reaction to autologous serum after plasmapheresis in all four tested patients is compatible with the idea that plasmapheresis acts by eliminating pathogenic autoantibodies from the circulation, although concrete evidence for this theory is lacking. Despite the somewhat favorable results of this study, the procedure is not used commonly in clinical practice. Case reports suggest efficacy in solar urticaria, particularly in cases in which there seems to be a circulating photoallergen [70].

Intravenous immunoglobulin

Given that a significant proportion of CU cases appear to be autoimmune in nature, intravenous immunoglobulin (IVIG), an agent that has some efficacy in other autoimmune conditions, might have a role in the treatment of CU. In an uncontrolled, open-label trial, 400 mg/kg/d of Sandoglobulin was given for 5 days to 10 patients with severe CU of an autoimmune nature (all patients had positive skin test responses to autologous serum) [71]. Two patients had complete and sustained remission (during 3 years of follow-up) after the single 5-day course of IVIG. Three patients had complete but temporary remission and relapsed after intervals of 6 to 21 weeks. Four patients had improvement (but not complete relief), and one patient had only slight transient improvement. Seven patients had a reduction in the size of the skin test response to autologous serum, suggesting that the IVIG might have blocked the autoimmune phenomenon in these patients. There have been no large-scale, double-blind, placebo-controlled trials of this agent.

Colchicine

Patients with urticarial vasculitis, who are generally refractory to treatment with H₁ antagonists alone and may be refractory to low-to-moderate doses of systemic steroids, may benefit from combined treatment with high-dose corticosteroids plus colchicine [72]. A case report describes dramatic improvement of normocomplementemic urticarial vasculitis with colchicine in a patient who was unresponsive to steroids [73]. There is little evidence of the use of colchicine in the treatment of ordinary CU.

Dapsone

Numerous case reports have shown benefit with dapsone for treatment of a variety of presentations of urticarial vasculitis [74–80], particularly the hypocomplementemic urticarial vasculitis syndrome. There are no reports of trials in ordinary urticaria, but given the evidence of efficacy for urticarial vasculitis, there may be some role for dapsone in severe cases of CU that seem to have some

clinical overlap with urticarial vasculitis. Dapsone is contraindicated in patients with G6PD deficiency.

Sulfasalazine

Open-label treatment with sulfasalazine, titrated up to a maximum dosage of 4 g/d, led to complete resolution of symptoms in two patients with severe delayed pressure urticaria [81]. Large-scale, controlled trials have not been reported.

Hydroxychloroquine

Case reports suggest that hydroxychloroquine can be helpful for hypocomplementemic urticarial vasculitis [82], and angioedema associated with acquired C1 inhibitor deficiency and systemic lupus [83]. Although this treatment has been used in clinical practice for ordinary CU, there are no reports of specific controlled trials.

Methotrexate

There are rare case reports of the use of methotrexate in CU. Gach et al described its use in two patients with severe CU who were refractory to treatment with antihistamines and required chronic steroid therapy to control their symptoms [84]. Neither patient had evidence of autoantibodies to the high-affinity IgE receptor using histamine-release assays. Significant clinical improvement was seen with 15 to 20 mg of methotrexate weekly. The potential toxicities of this agent need to be taken into account and make it unlikely that methotrexate will be used on a frequent basis in CU.

Cyclophosphamide

Although cyclophosphamide has been used for the treatment of urticarial vasculitis, reports of its use in CU treatment are scarce. Bernstein et al [85] reported a woman with severe autoimmune CU (established by a positive skin test to autologous serum) whose disease was unresponsive to most medications but could be controlled with prednisone at a dosage of 35 mg/d. She had developed steroid-related toxicity, so cyclophosphamide was started at an intravenous dose of 500 mg administered every 2 weeks and increased by 100 mg every 2 weeks until a maximum dose of 1500 mg was achieved, which was continued every 4 weeks. She was able to slowly taper and discontinue prednisone, and the autologous serum skin test turned negative (suggesting that the cyclophosphamide may have eradicated B-cell clones that were producing autoantibodies to the high-affinity IgE receptor). She had some mild residual symptoms but did not require further steroid treatment. This study is the only known report of the use of this agent in CU. Because of its significant immunosuppressive properties, cyclophosphamide is unlikely to be used by most clinicians in CU, except in extreme cases.

Interferon α

A single case report describes a favorable response to interferon α in a patient with chronic recurrent urticarial vasculitis and angioedema who was unresponsive to other agents [86].

Future directions and possibilities

As the treatment of allergic diseases continues to advance, new agents may be found that are effective in the treatment of urticaria. Some of these agents may turn out to be more effective than existing therapies, whereas others may be equally effective but have a more desirable safety profile.

Anti-IgE monoclonal antibodies

Considerable evidence has accumulated to support the hypothesis that a large proportion of cases of CU are caused by an underlying autoimmune phenomenon. Forty percent to 60% of patients have evidence of a serum histamine-releasing factor, manifested by a wheal-and-flare response when their own serum is injected intradermally (ie, a positive autologous serum skin test). Thirty percent to 50% of patients have a circulating autoantibody to the high-affinity IgE receptor, which is believed to be related to the ability of the serum to release histamine (and cause a positive autologous skin test). If these autoantibodies to the high-affinity IgE receptor are confirmed to be pathogenic in CU, specific targeting of this autoimmune process might be highly effective for the treatment of these patients. Treatment with omalizumab, a monoclonal antibody to IgE, has been shown to lead to decreased surface expression of the high-affinity IgE receptor on circulating basophils [87]. Whether this decreased expression would be seen on cutaneous mast cells is not known; if this effect were shown, one might hypothesize that omalizumab would be effective in patients who have the autoantibody to the high-affinity IgE receptor. No studies of the use of this drug for CU have been reported.

Specific targeting of autoantibodies to the IgE receptor

As further work is done to clarify the role of autoantibodies to the high-affinity IgE receptor in CU, other options for treatment may develop. If the autoantibodies are confirmed to be pathogenic, it may be possible to develop biologic agents to specifically target these IgE receptor-specific antibodies. As the technology of biologic therapy advances, this method may become feasible.

PDE4 antagonists

Phosphodiesterase 4 (PDE4) is an important cyclic adenosine monophosphate-metabolizing enzyme that is up-regulated in immune and inflammatory cells [88]. Second-generation PDE4 inhibitors are under development and have been studied for use in treating inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). One such agent, cilomilast, has been found to inhibit the release of some neutrophil chemoattractants (tumor necrosis

factor α , granulocyte-macrophage colony-stimulating factor) in patients with COPD [89]. Another PDE4 inhibitor, rolipram, has been found to enhance glucocorticoid-receptor function in vitro [90]. Roflumilast has been shown to have some efficacy in the treatment of allergic rhinitis [91]. A topical PDE4 inhibitor, cipamfylline, has been shown to be of some efficacy in the treatment of atopic dermatitis [92]. Whether these agents have a role in the treatment of CU has not been studied yet.

Summary

There have been a number of exciting developments in the treatment of allergic diseases. For some of the allergic conditions (eg, allergic rhinitis, asthma), several novel therapies have been developed, and other treatments are under investigation. The development of new treatments for urticaria has lagged behind. Although there are a number of options for the treatment of urticaria, there is still a need to develop better agents for this disease. For patients with CU whose disease is not controlled adequately with antihistamines, treatment options are limited. Systemic corticosteroids are effective in many patients, but the potential for long-term toxicity limits their use in chronic cases. Of the other agents that have been studied, those that have shown the most therapeutic efficacy can lead to side effects and potential long-term toxicity. Table 3 summarizes the pharmacotherapy options for CU in the form of a step-wise algorithm. With the ongoing development of novel agents for the treatment of allergic diseases, perhaps new agents will be discovered that are highly effective for the treatment of CU and safe for long-term use.

Table 3
Step-wise algorithm for the treatment of CU

Type of treatment	Recommended therapy
First line	H ₁ -receptor antagonists (antihistamines) 1. Second-generation agents may be preferable for chronic or daytime use 2. First-generation agents can be added in addition to second-generation agents if needed
Second line	H ₂ -receptor antagonist in combination with H ₁ -receptor antagonist
Third line	1. Consider increasing dose of H₁-receptor antagonist 2. Doxepin (for additional antihistamine effect) 3. Anti-leukotriene 4. COX-2 inhibitor 5. If evidence of thyroid autoimmunity, consider thyroxine
Fourth line	1. Chronic oral corticosteroids (titrated to lowest effective dose) 2. Cyclosporin A 3. Consider other nonstandard therapies: colchicine, dapsone, sulfasalazine, hydroxychloroquine, IVIG, plasmapheresis, interferon α, methotrexate, cyclophosphamide, calcium-channel blockers, warfarin, ephedrine, terbutaline

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