CME review

Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2

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Objective: To evaluate the use of alternative therapies for chronic urticaria refractory to first-line treatments in an evidence-based manner.

Data Sources: MEDLINE searches were performed cross-referencing *urticaria* with the names of multiple therapies. Articles were then reviewed for additional citations. Articles published after 1950 were considered.

Study Selection: All articles, including case reports, were reviewed for soundness and relevance.

Results: Experience has been reported for a wide variety of alternative therapies in the treatment of chronic idiopathic and physical urticarias. Evidence for most agents is limited to anecdotal reports. The therapies reviewed are also categorized based on criteria of safety, efficacy, convenience, and cost. The less preferred alternative agents in the second part of this review are divided between third-line therapies and others that are unable to be firmly recommended or that seem promising but lack substantial evidence.

Conclusions: Third-line alternative agents should be considered in patients with chronic urticaria who are severely affected and unresponsive to antihistamines and second-line therapies. Although monitoring for toxicity is important in management with third-line agents, safety remains favorable for most agents compared with corticosteroids.

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Off-label disclosure: Drs Morgan and Khan have indicated that most of the medications discussed represent off-label use, as mentioned in the article.

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INTRODUCTION

The second part of this review continues with alternative therapies for refractory chronic urticaria (CU) that are considered less preferred than previously surveyed second-line drugs, agents unable to be firmly recommended, and newer promising agents that lack substantial evidence. Criteria resulting in classification of these agents include potential for more serious adverse effects, evidence that is more limited or arguing against efficacy, inconvenience, intensive monitoring requirements, and high cost. Nevertheless, these less preferred alternative agents merit review, to foster understanding of the expanded management options available to clinicians. The term *alternative* is preferred for these therapies that may also be appropriately termed *immunosuppressive*, *immunomodulatory*, or *steroid sparing* because not all agents fit these descriptions in all circumstances.

Urticaria of chronicity longer than 6 weeks and with an autoimmune or idiopathic basis (CIU) will remain the focus of this review, alongside relevant experience involving physical urticarias, CU combined with a significant angioedema component, and urticarial vasculitis. Therapies for urticaria in the context of thyroiditis, *Helicobacter pylori*, herpesviruses, progestins, and Schnitzler syndrome exceed the scope of this discussion and are not reviewed.

In general, failure of first-line agents, such as high-dose or combination antihistamines, and adequate therapeutic trials of various second-line agents may prompt investigation into the appropriateness of third-line agents for individual patients with severe refractory CU. Corticosteroids remain the standard comparator for alternative therapies, such that criteria used to judge the merits of each alternative agent must be weighed against the high toxicity and lack of disease-modifying effect, yet high efficacy and low cost, of corticosteroids. Relevant practical variables, such as dosage and titra-

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tion, time to response, possibility of inducing remission, suggested monitoring, and level of evidence,[1] for each agent are given (Table 1). As with second-line agents, frequent follow-up by the clinician is important because of the need for close monitoring for toxicity in patients taking alternative agents for off-label use.

ALTERNATIVE THERAPIES FOR REFRACTORY CU: THIRD-LINE AGENTS

Androgens

Androgens are well established in treating hereditary angioedema but are less frequently used for CU. A major mechanism of action is stimulation of hepatic synthesis of various proteases.[2] Androgens may also exert anti-inflammatory effects by interfering with endogenous sex steroids[3] and suppressing leukocyte activation.[4] The first studies were performed in physical urticarias in which low levels of certain proteases were thought to be important. A randomized controlled trial[5] found danazol effective in 17 male patients with cholinergic urticaria, with a corresponding increase in α_1-antichymotrypsin. Other series[6,7] found similar efficacy. A case of aquagenic urticaria in a patient with human immunodeficiency virus responded dramatically to stanozolol.[8]

Androgens have also been studied in CIU. An early series[9] demonstrated varying degrees of symptom relief in 5 female patients receiving corticosteroids, with which stanozolol was suggested to have been synergistic. Recently, a relatively large (n = 58) 12-week, randomized, double-blind, placebo-controlled study[10] compared stanozolol, 2 mg twice daily, with placebo in patients with CIU refractory to cetirizine. The stanozolol group had a greater clinical response with respect to frequency of marked improvement (65% vs 29%) and mean reduction in clinical scores. Adverse effects were reported as "infrequent," with 2 patients having transient hypertransaminasemia that normalized without treatment cessation. This study is limited by little information on prior treatment and the observation that both groups seemed to have continued reduction in urticarial activity that had not plateaued at the end of the study.

Use of androgens may see particular application for physical urticarias. Androgens are disadvantaged by wide-ranging adverse effects that may affect numerous organ systems. Virilizing and dysmetabolic adverse effects may be distinctly troublesome, for which monitoring is recommended. Although androgens still compare favorably with corticosteroids in many situations, adverse effects, particularly with long-term use, limit their application to third-line status, especially in females.

Methotrexate

Methotrexate possesses anti-inflammatory, antiproliferative, and potentially immunomodulatory activities. Mechanisms relevant to urticaria include reduced neutrophil accumulation in inflamed skin,[11] diminished activated leukocyte adhesiveness and other adenosine-mediated anti-inflammatory properties,[12] decreased leukotriene synthesis,[13] and alteration in cytokine activity.[14] The earliest case report described a single patient with CIU with a long period of drug-free remission after methotrexate administration.[15] Another report[16] detailed 2 patients with CIU in whom second-line agents had failed but who responded to methotrexate within 1 to 2 weeks; however, both patients required maintenance methotrexate therapy for continued benefit. The researchers also mentioned knowledge of methotrexate failures. To our knowledge, the largest series[17] to date described 7 patients with CIU, all of whom seemed to achieve benefit within 1 to 2 weeks of starting methotrexate therapy. There was no comment on whether drug-free remission was seen, but the drug was well tolerated, with "few" adverse effects. The only other report involved a patient described as having urticarial vasculitis but whose biopsy result and clinical picture may also fit severe CIU. This case was notable for remission of at least 7 months after discontinuing a 4-month trial of lower-dose methotrexate (7.5 mg/wk).[18] One negative report[19] described exacerbation of urticarial vasculitis by methotrexate.

Based on a limited number of reports, methotrexate may be highly efficacious and capable of bringing about rapid and prolonged remission in certain patients. Because adverse effects may be serious and frequent monitoring is advised, methotrexate should be reserved for intractable cases in which other alternative agents have failed.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is the alternative agent with theoretically the most immunomodulatory potential in urticaria. Mechanisms of interest have been reviewed elsewhere but may include modulation of cell adhesion, immunoregulatory molecules, complement function, cytokine levels, autoantibodies, and anti-idiotypic networks, although the exact basis remains unclear.[20] Success was first reported in an open trial of 10 patients with CIU who were treated with 5 days of IVIG.[21] All were carefully selected, with positive autologous serum skin test (ASST) and basophil histamine-release test results. Other agents, including corticosteroids and various alternative agents, had failed in many of the patients. All patients were deemed to have had responses ranging from complete and lasting remission to modest transient benefit. The 3 patients who exhibited complete remission (1 after a second course) were symptom free at least 3 years after the last course of IVIG. The lowest dose described was 0.2 g/kg, repeated 1 day every 4 weeks, which produced benefit in a patient with CIU.[22] At a dose of 2 g/kg infused once, a different patient with CIU experienced benefit within 48 hours that lasted 7 months.[23] However, repeating the infusion produced only moderate benefit that failed to persist. In 2 other reports,[24,25] a 5-day infusion resulted in 2 complete responses, 1 partial benefit, and 1 failure among 4 patients with CIU. Failures have been reported elsewhere.[19,26]

The IVIG experience in physical urticarias is similarly limited. Clinical response has been documented in 5 of 8 patients with delayed-pressure urticaria (DPU), using 2 g/kg infused more than 2 to 3 days. Sustained remission was

Table 1. Third-Line Alternative Agents for the Treatment of Chronic Urticaria

Described doses and regimens according to class of agent	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[1]
Attenuated androgens						
Danazol, 400–600 mg/d orally (divided); or stanozolol, 1–5 mg/d orally (divided)	1 day to 2 weeks	Several days	+	Virilization, vasomotor symptoms, weight gain, and dysmetabolic features (hypertension, hyperlipoproteinemia, and cardiotoxicity); rarely, hepatotoxicity (hepatitis, cholestasis, and neoplasia), polychythemia, photosensitivity, and hemorrhagic cystitis; caution: females, children, thrombotic complications, and porphyria	Baseline: liver enzymes, lipoproteins, blood cell counts, urinalysis, and consider liver or spleen ultrasonography; follow-up: same, every 6 mo	Ib/B
Antifolate antimetabolite						
Methotrexate, 7.5–15 mg/wk orally; consider coadministration of folate	Several days to within 2 weeks	Within 2–3 weeks	+	Gastrointestinal complaints, stomatitis, marrow suppression, rash, hepatotoxicity, alopecia, and infections; caution: ensure dosing is understood to be weekly (not daily) and embryotoxicity	Baseline: blood cell counts, renal function, and liver enzymes; follow-up: blood cell counts monthly and renal function, liver enzymes every 1–2 months or more frequently in settings of increasing blood level or suspected toxicity	IIb/C
Immunoglobulin						
IVIG, 0.2–2.5 g/kg infused over 2–5 days; may require successive monthly courses	Several days to several weeks after starting	Several days to several months	++	Flushing, myalgias, headache, fever, backache, nausea, chest tightness, wheezing, and hemodynamic changes; rarely, aseptic meningitis and anaphylaxis	Baseline: blood cell counts, liver enzymes, renal function, and viral hepatitis studies; consider IgA level in some cases	IIb/C
Phototherapy						
Protocol varies by operator and UV modality	Several days to several weeks	Several days to several months?	++	Photoaging, cutaneous neoplasia, pruritus, dyspigmentation, nausea, headache, and fatigue; caution: photosensitivity disorder, porphyria, and coadministration of methotrexate or hydroxychloroquine	Baseline: skin examination; patients may need to wear UV-A–blocking eye protection; follow-up: same	Ib/C
Anticoagulants						
Warfarin, with target INR of ≥2; or heparin, 5000 U every 12 h	Several days	Several days	±	Hemorrhagic complications and osteoporosis (heparin); rarely, skin necrosis, cholesterol embolization, hepatotoxicity, and heparin-induced thrombocytopenia; caution: embryotoxicity	Baseline: INR for warfarin; consider blood cell counts and risk factors for bleeding complications; follow-up: same	IIb/C
Nitrogen mustard (alkylating agent)						
Cyclophosphamide, intravenously, 500 mg every 2 wk, increasing by 100 mg each successive pulse until 1500 mg/mo; often coadministered with dexamethasone and agents for prophylaxis of cystitis	1 to several months	Unknown	++	Gastrointestinal complaints, malaise, alopecia, marrow suppression, and stomatitis; rarely, rash, cystitis, delayed neoplasia, immune deficiency, and infertility	Baseline: blood cell counts, renal function, urinalysis, and liver enzymes; follow-up: periodic blood cell counts, urinalysis; maintain cumulative dose of <50 g	III/D

Continued

Table 1. Third-Line Alternative Agents for the Treatment of Chronic Urticaria (Continued)

Described doses and regimens according to class of agent	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[1]
Dihydropyridine calcium channel blocker						
Nifedipine (instant release), 5–20 mg orally every 8 h	Within 1 week	Several days	−	Hypotension and peripheral edema; rarely, flushing, lightheadedness, and gastrointestinal complaints	Baseline: blood pressure; follow-up: same	Ib/C
Gold salts						
Aurothiomalate, 10–100 mg/wk intramuscularly; start at low dose and increase weekly	Several doses (several weeks)	Unknown	+?	Gastrointestinal complaints, photosensitivity, stomatitis, rash, metallic taste, renal dysfunction, and anemia	Baseline: blood cell counts, renal function, and urinalysis; follow-up: blood cell counts and renal function every 1–4 weeks	III/D
Plasmapheresis						
Protocol varies by institution	Several days to several weeks	Several days to several months?	±	Fatigue, gastrointestinal complaints, fever, citrate toxicity (electrolyte disturbances, cramps, and numbness or tingling), and altered coagulation; rarely, humoral immune deficiency, anaphylaxis, and disruption of medication blood levels	Baseline: venous access, blood cell counts, electrolytes, renal function, liver enzymes, and coagulation times; follow-up: hemodynamics, cardiac monitoring, and electrolytes	III/C
Corticosteroid[a]						
Prednisone, up to 1 mg/kg/d (not to exceed 80 mg/d) or equivalent dose of other agent; titrate quickly to lowest effective dose	Several days to 1 week	Variable	−	Mood alteration, adipose and fluid weight gain, hypertension, hyperglycemia, hyperlipoproteinemia, cataracts, raised intraocular pressure, headache, gastrointestinal complaints, dermal atrophy, osteopenia, and infections; caution: children, preexisting psychiatric disorders, and diabetes	Baseline: consider glucose, mental status examination, blood pressure, and lipoproteins; follow-up: same, periodically	IV/D

Abbreviations and symbols: INR, international normalized ratio; IVIG, intravenous immunoglobulin; +, slight possibility; ++, may be expected in some patients; ± , unlikely; −, none; ?, a level of uncertainty regarding the drug in question because of sparse evidence.
[a] Listed for comparison purposes.

demonstrated in 3 patients, although 1 patient required multiple infusions.[27] A patient with solar urticaria had complete response after 3 courses of IVIG and remained disease free at 1-year follow-up.[28] Another patient required concomitant phototherapy for optimal benefit.[29] Favorable response in hypocomplementemic urticarial vasculitis has been reported recently.[30]

Intravenous immunoglobulin is a reasonably safe therapy familiar to many specialists who care for urticaria. Response seems to be rapid, with possibility of true disease-modifying effect in some responders. Adverse effects are generally predictable and manageable. The optimal dose and number of infusions to attempt are unclear. Based also on expense and inconvenience without better assurance of clinical benefit, IVIG should be considered a third-line therapy.

Phototherapy

Phototherapy comprises UV-A therapy with coadministration of psoralen (PUVA) or without coadministration of psoralen and UV-B therapy. Efficacy in phototherapy seems to be maximal for areas of irradiation, suggesting local mediators and cells as primary targets. Phototherapy may also decrease histamine release from mast cells.[31] One open trial[32] in solar urticaria found PUVA more effective than H_1 antihistamines. An earlier case report[33] described long-lasting remission after discontinuation. Another patient with solar urticaria who partially responded to PUVA but could not tolerate adverse effects improved while undergoing extracorporeal photochemotherapy daily for 2 days, then every 2 weeks for 8 months.[34] However, the patient relapsed 8 weeks after discontinuing photopheresis.

Phototherapy has also been studied in other physical urticarias and in CIU. The first such report[35] documented modest transient improvement using PUVA for CIU. Although PUVA is thought to add additional efficacy vs UV-A, a trial[36] with 19 patients with CIU found no difference between PUVA and UV-A, with both groups experiencing modest clinical benefit. A series[37] of 15 patients with physical urticarias (cold, cholinergic, and dermographic) responded better to broadband UV-B than those with CIU. A large retrospective series[38] of 88 patients with CIU showed benefit in 72% of courses of narrowband UV-B, including 27% of 95 courses with complete response. Telephone follow-up several years later revealed 33% remained clear and 45% had lasting benefit. Although phototherapy is often regarded mainly as a treatment for solar urticaria, other physical urticarias and CIU may derive a variable degree of clinical benefit when this modality is available. Some responders seem to enjoy long-lasting improvement.

Anticoagulants

Speculation about the intertwining role of coagulation and fibrinolysis with the inflammatory pathways in urticaria led to investigation of the role of drugs affecting coagulation. Antifibrinolytic and anticoagulant agents may act at various places in the coagulation-fibrinolysis-inflammatory cascades capable of shifting the balance away from prourticarial mediators.[39] Soon after the first report[40] investigating a kallikrein inhibitor in urticaria, a randomized controlled trial[41] using aprotinin revealed an impressive 81% response rate in 52 patients with a mixture of CIU, cold urticaria, acute urticaria, and angioedema. The response rate was higher if patients with acute urticaria were excluded. Best results were observed in atopic patients or in those with an angioedema component. Suggested mechanisms include inhibition of antibody formation and proteolytic enzymes, such as kallikrein (and its precursors) and C1 esterase inhibitor. Experience with tranexamic acid was described in an initial favorable report,[42] but also a small, negative, randomized, controlled trial.[43]

Anticoagulants have also been investigated. Thrombin is involved in selectin and interleukin (IL) 8 induction, leading to neutrophil adhesion and activation, so that thrombin inhibition may exert anti-inflammatory effects.[44] Heparinized autologous serum can reduce the urticarial response in the ASST, possibly by direct disruption of histamine-releasing factors.[45] The generation of thrombin, a protease able to activate mast cells, has also been associated with CIU.[46] Several case reports[47,48] have suggested efficacy of warfarin in CIU, including patients with a strong angioedema component. The only published trial[49] treated 8 patients with CIU with open-label warfarin titrated to an international normalized ratio of 2 to 2.5. Of 6 patients with benefit, 3 underwent a double-blind placebo-controlled trial of warfarin vs placebo for 4 months. Pruritus and angioedema scores significantly improved, but urticarial scores were not measured. The sole contradictory report[50] found that 3 of 4 patients with concomitant angioedema experienced no change or even worsened while taking warfarin. Subcutaneous heparin was reported to work rapidly and completely in a patient in whom warfarin and other alternative therapies had failed.[51] Benefit was highly dependent on continued dosing, with immediate relapse on cessation of home injections.

The potentially life-threatening hemorrhagic risk and need for frequent international normalized ratio monitoring relegate warfarin to third-line status. Similarly, heparin cannot be considered in many patients with intractable CIU. The case of response to heparin in which warfarin had failed suggests cross-efficacy should not be assumed. For the rare patient with CIU who has a simultaneous indication for anticoagulation, it may prove worthwhile to evaluate the efficacy of heparin or warfarin.

Cyclophosphamide

Cyclophosphamide has generally been reserved for patients in whom multiple other alternative agents have failed. Cyclophosphamide is thought to target plasma cells producing the autoantibody responsible for disease manifestations in autoimmune CIU[52]; this might explain the long latency period to and gradual character of clinical improvement noted in available reports. The first published reports described sustained remission in patients with urticarial vasculitis in whom numerous other agents had failed; after reaching the maximum cumulative dose, maintenance therapy with IVIG[53] or mycophenolate[54] was used. Evidence for CIU consists of 2 separate patients in whom multiple other alternative agents had failed. During an 8-month period, improvement began 4 weeks into the initial infusions and evolved into complete resolution by 6 months.[55] The patient continued to be asymptomatic 12 months after the last infusion. Another patient refractory to cyclosporine received cyclophosphamide orally at a higher dose, 1.5 mg/kg 5 days a week, yielding a total monthly dose of 2,000 mg/kg.[56] At 1 month, CIU severity was reduced 50% with nearly complete response at 6-month and 1-year follow-ups. Both patients converted to having ASST negative results. Low oral doses have also been tried in dermographic urticaria.[57] Failures have also been reported, although it is unclear if a sufficient dose or duration was used.[58]

In summary, cyclophosphamide may well be a highly effective and truly immunomodulatory therapy, but because of expense, inconvenience, need for monitoring, risk of serious adverse effects—including delayed secondary neoplasia and hemorrhagic cystitis—and relative paucity of published evidence, this agent should be reserved as a last resort.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers are not generally considered immunomodulatory or immunosuppressive agents, yet by serendipity, nifedipine attracted interest as a potential antiurticarial agent. The mechanism of action is unclear but may involve inhibition of stimulated T-lymphocyte proliferation[59] and mast cell mediator release.[60] Although

early cases suggested efficacy,[61,62] the 2 available randomized controlled trials yielded conflicting results. The first examined 18 patients with symptomatic dermographism and found no response at either 5 or 10 mg thrice daily. The researchers speculated that the dose used may have been too low.[63] A different randomized, controlled, crossover trial demonstrated benefit in 7 patients with CIU taking doses up to 20 mg thrice daily.[64] Notably, patients experienced mild adverse effects attributable to nifedipine.

Interest in calcium channel blockers seems to have waned since these reports. Fairly rapid response after achieving the target dose, relative familiarity with prescribing, and wide availability are advantages. Relatively frequent adverse effects relating mostly to hemodynamics and requirement for blood pressure monitoring are disadvantages, but a trial might be reasonable for patients with CU with concurrent indications for this class of drug.

Chrysotherapy

Gold salts constitute an infrequently used agent for urticaria. Mechanisms include suppression of cellular and humoral immunity and other anti-inflammatory actions, such as inhibition of lysosomal enzymes, suppression of prostaglandin synthesis, and modulation of initial complement component function.[65] Only 1 published case[66] described efficacy for a patient with urticarial vasculitis at the low dose of 10 mg/wk. This patient had previously responded to dapsone but discontinued this therapy because of adverse effects. Although gold may be effective in some patients, perhaps at lower doses than used elsewhere, and has some potential for immunomodulatory action, paucity of evidence, adverse effects, need for monitoring, and expense argue for trying other alternative agents first.

Plasmapheresis

Like phototherapy, plasmapheresis has been mostly associated with treatment of solar urticaria. The mechanism of action is thought to involve removal of autoantibody ("serum factor") and inflammatory mediators.[67] As a predictive factor, most authorities recommend plasmapheresis for serum factor–positive solar urticaria; a small comparison demonstrated modest benefit in 2 serum factor–positive patients but none in 1 serum factor–negative patient.[68] Various case reports[69,70] have demonstrated clinical benefit as soon as the first day in some patients, but the possibility of long-term remission has been observed less consistently. Phototherapy has also been combined with plasmapheresis to convert partial response into full remission.[71] Only 1 series[72] has examined plasmapheresis for CIU, in which 3 of 8 patients derived modest benefit. However, most eventually relapsed, because of hypothesized reaccumulation of autoantibody. Plasmapheresis may be appropriate for refractory solar urticaria with positive serum factor and when pharmacotherapy and phototherapy have failed. For CIU, modest efficacy, expense, inconvenience, and limited experience restrict the use of plasmapheresis to exceptional circumstances.

ALTERNATIVE AGENTS NOT CURRENTLY RECOMMENDED

A variety of other alternative therapies cannot be recommended because of lack of published positive experience. Azathioprine has been used in many parallel indications with other alternative agents; however, no direct published reports or trials are available for CU. Indirect references in other reports, mostly for urticarial vasculitis, have been uniformly disappointing.[19,26,53]

Several asthma medications have also been used for urticaria, with mixed results. Cromolyn has been attempted for nonsteroidal anti-inflammatory drug (NSAID)– and food additive–induced urticaria unsuccessfully.[73,74] One positive report[75] of benefit with inhaled cromolyn in 3 patients with CIU who did not have asthma has not been duplicated. β-Agonists may suppress the wheal-and-flare response[76] and have also been used for CIU and physical urticarias. Terbutaline, up to 25 mg thrice daily, was found effective where antihistamines had failed; among 24 patients, those with CIU had more benefit than those with physical urticarias.[77] The only other favorable reports[78,79] described patients with cold and other urticarias refractory to antihistamines who had benefit while taking a combination of ketotifen and terbutaline. However, other open series[76,80] found no benefit. A randomized, double-blind, multiarm, crossover study[81] found terbutaline inferior to antihistamines in 19 patients with CIU. From data to date, neither cromones nor β-agonists represent effective therapies in the treatment of CIU.

Available published data on methylxanthines suggest the possibility of benefit but with wide variability in degree of response. In the earliest report,[82] only 3 of 15 patients (20%) with CIU experienced complete response after a 4-week course of theophylline, whereas 6 (40%) had no significant response. A recent, double-blind, placebo-controlled study[83] of 134 patients with CIU receiving maintenance cetirizine showed moderate benefit in the group treated with add-on theophylline compared with placebo. The 54 patients who completed the theophylline group exhibited reduction in overall visual analog scores but not pruritus. Several weeks seemed necessary for benefit to become apparent.

Experience in physical urticarias is similarly mixed. Benefit for DPU was demonstrated in an open crossover trial of 23 patients. Response became apparent around the second month for the theophylline plus cetirizine group; benefit required continuation of medication in responders. A combination of aminophylline plus terbutaline showed a wide spectrum of response in 42 patients with cold urticaria; 5 had complete response by 1 week, and 2 had no apparent benefit, with the remainder having modest benefit after more than 2 to 6 months of open follow-up therapy.[84] Adverse effects were significant, with 3 having cardiac events that mandated cessation of therapy and 19 others having less severe problems. Although these studies suggest a long period of therapy may yield benefit, this seems to be in a few patients and modest overall. These data seem to support prevailing opinion that

theophylline might be at best modestly effective but has significant liability for adverse effects and requires monitoring of drug levels.

Indomethacin is the main NSAID studied for use in physical urticarias and urticarial vasculitis. Benefit has been most consistent in patients with pain and constitutional symptoms.[85,86] These benefits may primarily be because of an analgesic rather than antiurticarial effect. Studies[87,88] suggesting efficacy of rofecoxib in CIU have not been replicated with available selective cyclooxygenase inhibitors. Combined with the well-known propensity for NSAIDs to trigger urticaria in certain patients, they are unable to be recommended for general use in CU without further study.

Interferon alfa has shown disappointing results in 2 published series of patients with CU. A regimen of 3×10^6 U thrice weekly for 8 weeks failed to benefit patients with a mixture of CIU, DPU, and cold urticaria.[89] In another open trial,[90] 4 of 8 patients with CIU achieved partial response; however, efficacy seemed to diminish over time. The sole successful report[26] described a patient with urticarial vasculitis in whom numerous alternative agents had failed but who achieved benefit with interferon alfa-2a. Considering the expense and potential for troublesome adverse effects without better evidence for efficacy, use of interferon alfa for CU must be advised against.

Autohemotherapy involves parenteral injection of autologous blood in an attempt to desensitize patients to endogenous prourticarial factors thought to be implicated in CIU. After an initial promising report,[91] the first formal investigation for CIU has recently been published. In this single-blind placebo-controlled trial, 56 patients with CIU were randomized to either autologous, whole, untreated blood, 5 mL intramuscularly (2.5 mL the first week), or isotonic sodium chloride solution for 8 weeks.[92] Patients with ASST positivity experienced moderate reduction in urticarial lesions, decreased antihistamine use, and improved quality of life. The ASST-negative patients did not have appreciable benefit. It is advisable that additional favorable evidence should be accumulated at more centers before autohemotherapy can be widely considered in the treatment of refractory CIU.

There remains no evidence that allergens play a role in CU other than in unusual circumstances. Immunotherapy to sweat extract has been reported to be successful in the treatment of cholinergic urticaria, presumably because of induction of tolerance to endogenous allergens.[93] A single report[94] describes a case of CU due to grass pollinosis, treated successfully with desensitization. Seasonal CU occurring during the grass season, with severity beyond ordinary contact urticaria to grass, resolved after the patient achieved the maintenance dose of Timothy grass. This curiosity aside, routine aeroallergen testing and immunotherapy continues not to be indicated in the management of CIU.

OTHER PROMISING AGENTS WITHOUT SUFFICIENT EXPERIENCE

Several biological agents that seem promising but are too new to have sufficient experience to warrant inclusion among second-line agents are briefly discussed herein. The first published use of omalizumab**,** a monoclonal antibody directed against IgE, has been reported for cold urticaria.[95] An 11-year-old girl with cold urticaria and extrinsic asthma, both refractory to conventional therapy, experienced partial response between 2 and 4 weeks after the initial dose. Progression to complete response occurred after 5 months. Relapse occurred on missing 1 month of injections, with prompt restoration of benefit after resuming therapy. Expense and inconvenience remain barriers to broader application, but of the agents lacking more evidence, omalizumab seems most promising based on speculation that patients with CIU with circulating IgE or IgE receptor autoantibodies might experience similar benefit.

Inhibitors of tumor necrosis factor α (TNF-α) and IL-1 have recently shown promise. After 5 days of etanercept, 25 mg twice weekly, for refractory psoriasis, DPU symptoms resolved completely in a patient whose symptoms were only partially controlled with cetirizine.[96] After 5 months, this patient was switched to infliximab for better control of psoriasis and remained free of DPU symptoms while receiving this agent at 1-year follow-up. Similarly rapid impressive benefit was noted in 1 patient with urticarial vasculitis after starting anakinra, an antagonist of IL-1.[97] No adverse effects were noted with either treatment. Because TNF-α has been shown to be up-regulated in lesional and nonlesional skin in various types of CU,[98] inhibitors of TNF-α and IL-1 may indeed be effective agents, but further experience is required.

Rituximab is another biological therapy of potential interest for autoantibody-mediated disorders. B lymphocytes are targeted, similar to cyclophosphamide, but with the potential for fewer adverse effects. One report[99] detailed a patient with hypocomplementemic urticarial vasculitis in whom cyclophosphamide, prednisone, and other alternative agents had failed. A 4-week course of rituximab, 375 mg/m^2, caused "rapid" improvement, with tapering of corticosteroids and drug-free remission from the urticaria/angioedema of unspecified duration. No adverse effects were observed. However, the same regimen administered to a patient with CIU in whom numerous alternative therapies had failed resulted in no improvement.[100] Rituximab seems to be an interesting alternative agent, but results of published experience are mixed and limited.

CONCLUSION

Third-line therapies retain value and interest in the management of CU refractory to antihistamines and second-line agents. In most situations, third-line agents can be appropriate and preferable to systemic corticosteroids. The practitioner with sufficient skill and knowledge may successfully apply third-line agents and others we have not classified as recom-

mended safely and appropriately for selected patients with CU.

Clearly, interest in broadening the pharmacologic armamentarium is not a recent phenomenon. A review[101] from half a century ago describes a bewildering variety of alternative treatments for CU. The level of evidence for many of these formulations would not meet the least rigorous of today's standards, but evidence for several agents that continue to appear in our list has improved only marginally in the past 50 years. Future management of CU will be challenged to improve therapy for disease refractory to standard medications through further elucidation of the underlying pathophysiological features and clinical trials to bolster evidence for many promising but understudied therapies.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor medical education for physicians. ACAAI designates each Annals CME Review Article for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credits commensurate with the extent of their participation in the activity.

CME Examination

1–5, Morgan M, Khan DA. 2008;100:517–526.

CME Test Questions

1. Which of the following medications has demonstrated efficacy for chronic urticaria in a randomized controlled trial?
   a. cyclophosphamide
   b. intravenous immunoglobulin (IVIG)
   c. methotrexate
   d. stanozolol
2. B-lymphocyte suppression is a major mechanism of action for which of the following medications?
   a. infliximab
   b. omalizumab
   c. natilizumab
   d. rituximab
3. Which of the following therapies has the lowest level of evidence for efficacy in chronic urticaria?
   a. azathioprine
   b. nifedipine
   c. phototherapy
   d. warfarin
4. Which of the following therapies would likely be most efficacious in a patient with solar urticaria?
   a. cyclophosphamide
   b. danazol
   c. methotrexate
   d. phototherapy
5. Delayed secondary neoplasia is a potential adverse effect seen most commonly with which of the following therapies?
   a. cyclophosphamide
   b. etanercept
   c. IVIG
   d. stanozolol

Answers found on page 544.