

Immunomodulatory Approaches to the Management of Chronic Urticaria: An Immune-Mediated Inflammatory Disease

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Current Allergy and Asthma Reports 2008, **8**:277–287
Current Medicine Group LLC ISSN 1529-7322
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Although commonly encountered in clinical practice, chronic urticaria (CU) remains difficult to treat. In contrast to acute urticaria, neither exogenous triggers nor specific immunoglobulin E are identified in most chronic cases. A body of evidence suggests that CU is represented within the spectrum of immune-mediated inflammatory diseases (IMID). Our understanding of the CU disease pathogenesis now recognizes a role for T cells, B cells, and autoantibodies, and intrinsic abnormalities of histamine-releasing effector cells, thus providing new targets of intervention beyond the current mainstay of often inadequate symptomatic treatment directed against histamine receptors and steroids, with their attendant morbidities. Agents previously used to treat other autoimmune and inflammatory diseases have demonstrated efficacy in CU. Newer biologic and nonbiologic immunomodulatory agents approved for other indications and in clinical development provide potential options for this often severe disease.

Introduction

Chronic urticaria (CU) remains a vexing problem for patients and clinicians, with a significant unmet medical need for effective treatment. Many patients experience unrelenting symptoms that significantly interfere with activities of daily living. Recent reviews have highlighted the effect of urticaria on quality-of-life scores, noting

impairment as high as psoriasis and atopic dermatitis [1•]. Moreover, the costs of treating CU are similar to those associated with bullous skin diseases [2•]. Medical management is usually grounded in symptom-blocking therapies directed against histamine (via both H₁ and H₂ receptors), and sometimes cysteinyl leukotriene receptor antagonists, with variable effectiveness [3].

Despite maximal approved (often suprathreshold) doses of antihistamines and soporific drug combinations, many patients with CU have refractory symptoms. Most patients respond to moderate to high doses of corticosteroids; however, many patients promptly relapse upon discontinuation or tapering below a threshold steroid dose. Morbidities from chronic steroids are significant—weight gain, fat redistribution, osteoporosis, hyperglycemia, hypertension, cataracts, and osteonecrosis. Some patients with CU remain refractory even to chronic steroids.

CU lasting more than several weeks (in contrast to acute and self-limited cases) is rarely a consequence of identifiable exogenous triggers. Neither careful history nor specific immunoglobulin (Ig) E testing reveals etiology, and elimination diets and specific allergen avoidance are frequently unsuccessful. The prevalence of atopic disease is not significantly increased in CU, arguing against an allergic diathesis in the condition [4••].

Immunologic Aberrancies in Chronic Urticaria

Patients with CU have several immunologic abnormalities. An association of CU with thyroid autoimmunity is recognized as a higher prevalence of thyroid autoantibodies (either antithyroid peroxidase or antithyroglobulin) in patients with CU than in controls [5]. No clear evidence exists that antithyroid antibodies are pathogenic in CU; rather, their presence may serve as an autoimmunity marker. Other autoantibodies—antinuclear antibodies, antiparietal cell antibodies, anti-intrinsic factor, and antiadrenal antibodies—have been seen in CU, suggesting at least “guilt by association” with other autoimmune conditions. Like other

Table 1. Examples of immune-mediated inflammatory diseases

Rheumatoid arthritis	Sarcoidosis
Systemic lupus erythematosus	Crohn's disease
Sjögren's syndrome	Ulcerative colitis
Ankylosing spondylitis	Celiac disease
Vasculitis	Diffuse proliferative glomerulonephritis
Scleroderma	Antiglomerular basement membrane disease
Thyroid (Hashimoto's, Grave's)	Psoriasis
Myasthenia gravis	Bullous skin disease
Multiple sclerosis	Chronic urticaria
Dermatomyositis	Atopic dermatitis
Idiopathic thrombocytopenic purpura	Asthma

autoimmune conditions, there is a gender predilection for women, with disease onset typically in childbearing years. Major histocompatibility complex (MHC) class II associations similar to those seen in other autoimmune diseases, notably HLA-DR4, were described in patients with CU [6].

Several groups have described antibodies against IgE or against the extracellular domain of high-affinity IgE receptor (FcεRIα) in 40% to 60% of CU cases [7]. First described when histamine-releasing activity was isolated from the IgG fraction of serum, these antibodies elicit mast cell and basophil degranulation, suggesting a functional role for some antibodies. Previous studies suggested a higher prevalence of complement-fixing isotypes in CU, and proposed that functional activity of these antibodies is dependent on complement, most notably C5a [7••]. One group also described autoantibodies directed against the low-affinity receptor for IgE, FcεRII (CD23), in patients with CU that induces eosinophil degranulation [8•].

Relevance of these antibodies to urticaria pathogenesis remains unclear because they have been detected in patients without CU, and assays are not standardized [9,10••]. In other autoimmune diseases, however, a pathogenic or functional role for detectable antibodies is unknown. Thus, whether the detected anti-FcεRI and anti-IgE antibodies are simply markers of an underlying autoimmune state, or truly pathogenic, remains undetermined.

Notwithstanding reservations concerning autoantibodies that cause mast cell and basophil degranulation as an explanation for CU, other factors suggest an autoimmune diathesis, including biopsies with a mixed cellular infiltrate often containing T cells, expression of proinflammatory cytokines, absence of atopic disease, and association with frequent systemic symptoms (arthralgias, arthritis, fatigue, elevations of acute phase reactants) in the absence of a more classic autoimmune disease or biopsy demonstrating vasculitis.

In addition to abnormalities in the upstream effector immunity arm (eg, antigen-driven, immunologically mediated), emerging data suggest that dysregulation of signaling pathways through effector histamine-releasing cells may also be important in CU. Increased basophils at the lesion site with peripheral blood basopenia have been recognized. Older studies demonstrated increased mast cell numbers in lesional and nonlesional skin of patients with urticaria, but others have not confirmed this finding. However, mast cells and basophils were shown to have increased releasability to agonists [11•]. Finally, upregulation of adhesion molecules on endothelial cells has been demonstrated in CU, likely contributing to the infiltrates of lymphocytes, neutrophils, and eosinophils [12].

Given the recognition of chronic urticaria as an immunologically mediated and possibly autoimmune condition, and the adverse consequences of long-term steroid treatment, many have used therapies that affect various aspects of immunologic function for steroid sparing and symptomatic improvement. Treatment of autoimmune diseases now includes several therapies that are far more targeted in effects than traditional immunosuppressive agents and are approved or under study for various indications.

In the remainder of this review, we consider studies of various immunomodulatory drugs for CU and the development of a paradigm for urticaria as an immune-mediated inflammatory condition that may allow future application of more targeted immunotherapeutics.

Immune-Mediated Inflammatory Diseases

The concept of immune-mediated inflammatory diseases (IMID) has evolved with the recognition that diverse diseases, previously viewed only in the context of organ-based inflammation, share many pathogenic features [13•]. With pathogenic understanding moving forward at cellular and molecular levels, common mechanisms are appreciated across disease processes (Table 1). This has been even more evident as targeted therapies directed against a particular cytokine or cell receptor demonstrate efficacy across a range of conditions, as seen with tumor necrosis factor (TNF) antagonists in rheumatoid arthritis, psoriasis, and Crohn's disease, or with rituximab, a B-cell depleting agent developed for lymphoma, now shown to be effective in rheumatoid arthritis, lupus, bullous skin disease, and idiopathic thrombocytopenic purpura.

In most circumstances, the IMID concept involves hypothesized susceptibility factors (eg, genetic) with an immunologic activation event driven through exposure to various exogenous or modified endogenous triggers (Fig. 1). This is often demonstrated by increased antigen-presenting cells expressing surface MHC, and the finding of activated T lymphocytes, often with proliferation restricted to a limited set of clones. T-cell activation results in release of cytokines, which act on other effector cell types. In different diseases, the T-cell populations and phenotypes may be different,

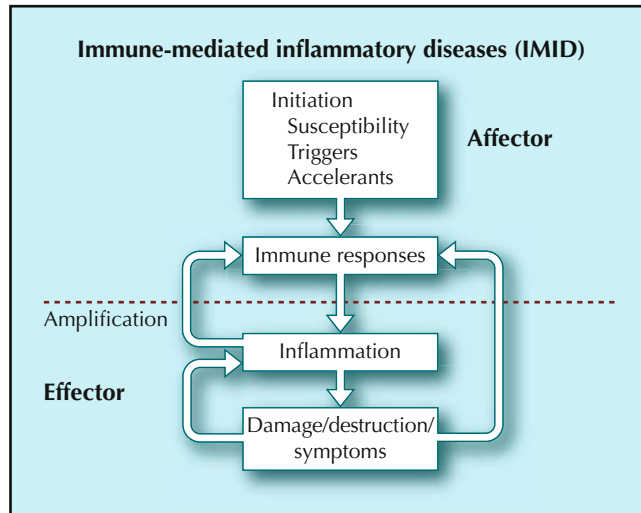


Figure 1. Immune-mediated inflammatory diseases.

with some diseases showing CD4⁺ T cells and others CD8⁺ T cells. In diseases such as asthma, T cells demonstrating a T-helper (Th) type 2 cytokine profile (eg, interleukin [IL]-4, IL-5, IL-13) are seen, which support the generation of IgE and an atopic phenotype characterized by mast cells, eosinophils, and basophils. Alternatively, a Th1 cytokine profile (interferon [IFN]- γ , IL-12, and TNF) is seen in rheumatoid arthritis, psoriasis, and inflammatory bowel disease, which have as common features macrophage activation and cytokine and mediator release. These effector cells may be tissue specific and result in the end-organ damage and symptoms associated with different disorders.

Clearly, the Th1/Th2 paradigm is more complex in human diseases, with many conditions demonstrating aspects of both (eg, TNF's role in asthma) [14••]. Furthermore, as diseases persist over time, they may develop autocrine positive feedback or autoamplification loops, leading to ongoing inflammation even when the initial insult is gone.

Chronic Urticaria as an IMID

In CU, the source of antigenic exposure is often unclear. Acute urticaria is seen with identifiable exogenous triggers (eg, food or drugs) and with acute bacterial or viral infection. Some patients track onset of CU symptoms to an initiating infectious event, but symptoms persist after treatment and resolution of the infection. Infectious initiators have been described in other autoimmune diseases through mechanisms such as molecular mimicry, innate immune responses with activation of acquired immunity, or effects of cytokines (eg, INF) increasing general immunologic activation [15••]. Few studies have evaluated genetic susceptibilities in CU; however, one group showed increased expression of certain class II MHC alleles, particularly those associated with other autoimmune diseases, notably HLA-DR4 [6]. Local increases in MHC class II expression in CU lesions have been reported

[16]. Another group recently described class I HLA-B44 associated with aspirin-induced urticaria, but did not perform extensive analysis of class II alleles or extend their study to CU [17].

The evidence for T-cell activation in CU is supported by biopsies from lesional skin with increased mononuclear and T cells with a Th0 phenotype and expression of IFN- γ and IL-4, in contrast to the Th1 phenotype of allergen-induced late-phase responses [18]. In CU, an increased number of peripheral activated CD45RO⁺ T cells have been correlated with wheals [19]. Another study reported that circulating T cells of patients with CU had increased expression of CD40L, in concert with increased *bcl-2* expression in T and B cells, indicating an activated phenotype [20]. Similarly, patients with active idiopathic anaphylaxis have an increased number of circulating activated T cells [21].

The demonstration of antibodies recognizing cell surface receptors or IgE in CU provides additional indirect evidence of T-cell and B-cell activation. The presence of other autoantibodies in some patients with CU further implicates a role for B cells. Proposed mechanisms for ubiquitous endogenous proteins becoming antigenic are poorly understood, but may be due to breaks in tolerance, altered compartmental expression, post-translational modifications, conformational changes, or coexpression with neoantigens. In some classic autoimmune diseases, antibodies are directly responsible for disease manifestations (eg, antiplatelet antibodies in idiopathic thrombocytopenic purpura, anti-double-stranded DNA antibodies in lupus nephritis, anti-Ro in congenital heart block and neonatal lupus). However, in other diseases, autoantibodies represent epiphenomenon of immunologic activation (eg, rheumatoid factors and anti-cyclic citrullinated peptides in RA, and the questionable role for antineutrophil cytoplasmic antibody in vasculitis).

The primary effector cells in urticaria are Fc ϵ RI-bearing mast cells and basophils [11•]. Resident cutaneous mast cells release preformed and newly synthesized inflammatory mediators including histamine, leukotriene C₄, prostaglandin D₂, proinflammatory cytokines (including TNF), and proteases. Under the IMID model, these cells may be activated directly via antibodies against Fc ϵ RI, antibodies against cell-bound IgE, and through other receptors, such as the C5a receptor (CD88) or the stem cell factor receptor *c-kit* (CD-117). Skin mast cells of the MCTC phenotype have been shown to express C5a receptors [7••,22].

Basophils have been implicated in CU, with increased expression of activation markers such as CD203c in response to urticaria sera [23], intrinsic upregulation of histamine release of basophils from some patients, suggestions of a primed cell phenotype in patients with positive autologous skin tests [24], circulating basopenia, lesional basophil infiltration, and augmented releasability of basophils. Different functional profiles of basophils have been described in CU; some are easily activated through

FcεRI, whereas others are resistant. These phenotypic differences have been linked to differential expression of the regulatory phosphatases SHIP-1 and SHIP-2, suggesting intrinsic signal transduction mechanisms as an explanation for some CU cases [25]. Other cells seen at lesional sites include lymphocytes, other mononuclear cells, and variable numbers of eosinophils and neutrophils—the last two implicated in CU pathogenesis and symptoms [26,27]. Recruitment of other effector cells is likely multifactorial, involving chemokine release, other chemotactic factors, adhesion molecule upregulation, and various vasoactive mediators [28].

Experience with Immunomodulators and Potential Targets in Urticaria

For most CU patients, treatment goals are to improve the symptom of itching and avoid cosmetic disfigurement from skin lesions and angioedema; unfortunately, antihistamines are often ineffective. Corticosteroids control symptoms in many patients, but may require significant doses. Many immunomodulatory approaches have been used, with case reports, case series, and rare randomized trials reporting efficacy; however, currently antihistamines are the only drugs approved in the United States for chronic urticaria. By understanding urticaria within the IMID framework discussed previously, each step in the disease can be evaluated to better understand the rationale for using a particular agent or agents currently approved for other diseases and others in development (Fig. 2).

Antigen presentation

The proximal event in autoimmune disease initiation is the presentation of antigen to T cells. Several drugs have effects in these upstream steps. Hydroxychloroquine (Plaquenil; Sanofi-Aventis, Bridgewater, NJ) has been used to treat systemic lupus and rheumatoid arthritis for many years. Developed as an antimalarial agent, hydroxychloroquine has effects on lysosomal vacuolar antigen processing, MHC trafficking, and antigen presentation [29•]. Antimalarials also inhibit phospholipase A₂ and may affect granule release in mast cells and neutrophils [30]. More recently, effects of hydroxychloroquine on intracellular Toll-like receptors were recognized [29•]. One randomized, placebo-controlled study of hydroxychloroquine was done in 18 patients with CU. At 12 weeks, quality of life and global symptom severity score improved, but the dose administered was not reported [31]. The dose of hydroxychloroquine typically used in other autoimmune diseases is 400 mg/d. Additional case reports of efficacy exist for antimalarials in delayed pressure urticaria and hypocomplementemic urticarial vasculitis. Although extremely rare at doses less than 6.5 mg/kg/d, the major concerning drug toxicity is ocular, and patients should see an ophthalmologist when beginning treatment and periodically thereafter.

T-cell-directed therapies

Therapies directed against T cells have been used in a range of autoimmune conditions. Drugs include cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide.

Cyclosporine and tacrolimus (FK506)

Most reports of T-cell agents in CU have been with calcineurin and cyclophilin inhibitors, cyclosporine, and tacrolimus (FK506). Originally developed to prevent transplant rejection, these agents are potent T-cell immunosuppressants that act on signal transduction via nuclear factor of activated T cells and transcription of genes such as IL-2 and IL-4. Additional effects have been described in mast cells and basophils with inhibition of granule exocytosis through effects on intracellular calcium flux [32•]. Cyclosporine (Neoral; Sandimmune; Novartis, Annandale, NJ) is approved for use in rheumatoid arthritis and has been used in other autoimmune diseases.

Two randomized trials of cyclosporine in CU have been reported. Thirty patients treated with cyclosporine (4 mg/kg) for 4 weeks demonstrated improvement compared with placebo in clinical urticaria activity, reduction in basophil histamine release from CU serum compared with baseline, and the size of wheals in response to autologous skin tests from treated serum versus baseline serum [33]. Vena et al. [34•] reported a second randomized controlled trial of cyclosporine in which 99 patients with CU were treated with 5 mg/kg, tapered to 4 mg/kg at 2 weeks, then to 3 mg/kg through 24 weeks. At 8 weeks, urticaria severity was reduced (reduction was maintained at 16 weeks), and Dermatology Life Quality Index scores were improved. Notable side effects were increased creatinine in 19% and hypertension in 6% of the patients treated.

Another group recently reported an open-label experience of tacrolimus (FK506, Prograf; Astellas Pharma US, Deerfield, IL) in 19 patients with severe CU [35•]. Patients were initially treated for 4 weeks with approximately 4 mg/d, followed by 6 weeks at approximately 2 mg/d, then 1 mg/d through 12 weeks. Symptoms improved in 70% of patients, with 47% discontinuing antihistamines and 10% discontinuing steroids. Toxicities were notable for gastrointestinal (GI) complaints, but there were no reports of neurologic symptoms, increased creatinine, hypertension, or infection often associated with the drug. Although the reports are encouraging, potential toxicities are considerable and include immunosuppression and longer term lymphoproliferative disease, hypertrichosis, and gingival hyperplasia. Several medication interactions may exacerbate toxicity.

Mycophenolate mofetil

Mycophenolate mofetil (Cellcept; Roche, Nutley, NJ) is another immunosuppressant developed for transplant and increasingly used in lupus nephritis. The drug

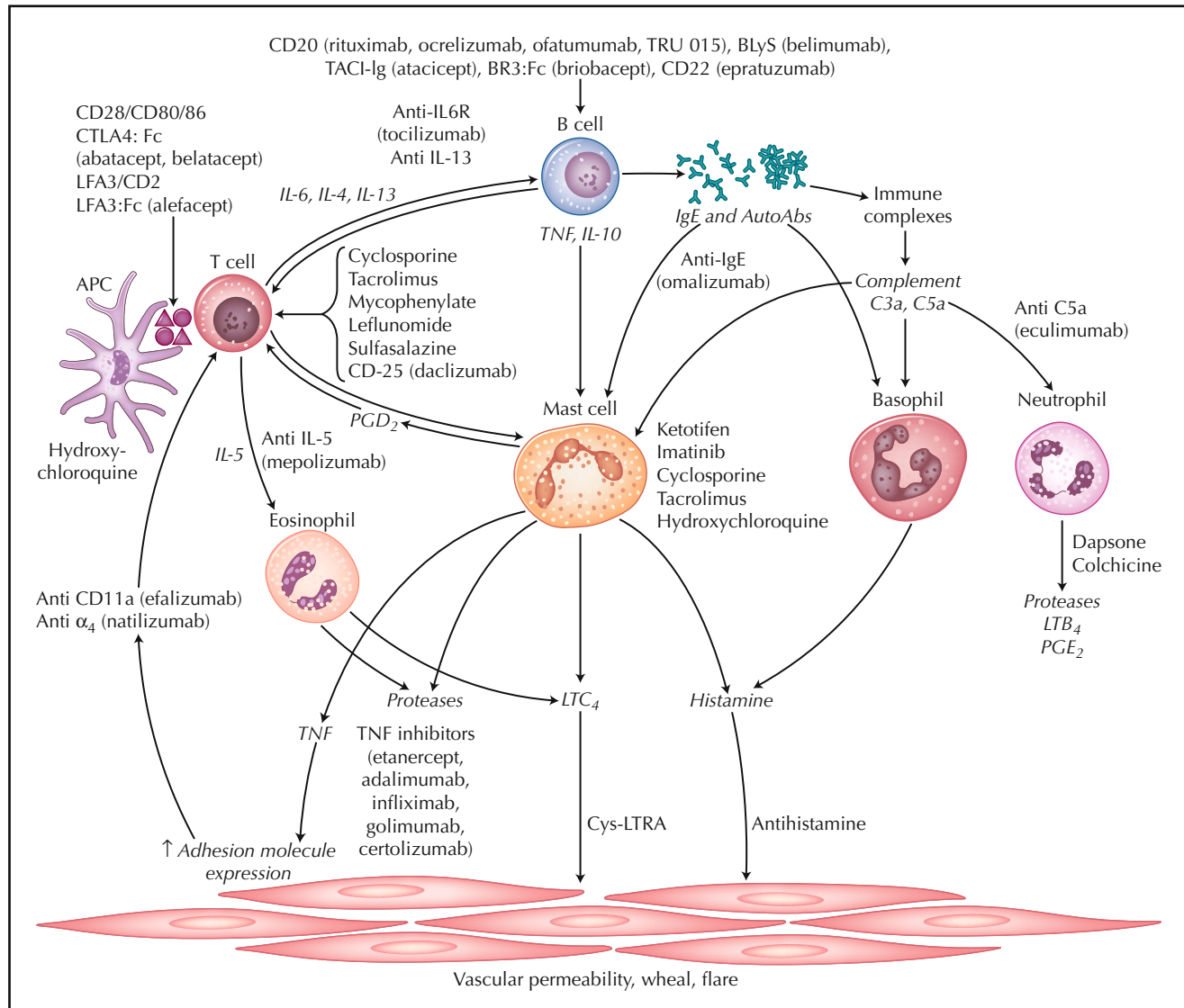


Figure 2. Chronic urticaria as an immune-mediated inflammatory disease: targets of therapy. Ig—immunoglobulin; IL—interleukin; LT—leukotriene; PG—prostaglandin; TNF—tumor necrosis factor.

inhibits inosine monophosphate dehydrogenase in the de novo synthesis of guanosine nucleotides. The net effects are reduced T-cell numbers and function and decreased antibodies. A recent study reported open-label experience in nine patients with CU who were treated with 1000 mg, twice daily, for 12 weeks. There was a progressive reduction in urticaria activity, wheal, and itch scores by 6 weeks, which allowed tapering of corticosteroids and antihistamines through 12 weeks. Responses were maintained through an additional 6 months [36•]. No toxicities were noted; however, in other studies of this drug, dose-limiting GI complaints of nausea and diarrhea occurred in up to 20% of patients, and cytopenias were seen [37].

Cyclophosphamide

Cyclophosphamide (Cytoxan; Bristol-Myers Squibb, Princeton, NJ) is a potent alkylating immunosuppressant

used to treat lupus nephritis, severe vasculitis, and many malignancies; it was effective in two patients with CU. Toxicities of this agent are substantial and include ovarian failure, azoospermia, hemorrhagic cystitis, cytopenias and marrow suppression, bacterial and opportunistic infection, GI intolerance, alopecia, and secondary malignancy. Therefore, it should be considered a treatment of last resort for CU.

Azathioprine and 6-mercaptopurine

Azathioprine (Imuran; GlaxoSmithKline, Philadelphia, PA) and 6-mercaptopurine (Purinethol; Teva Pharmaceuticals, North Wales, PA) inhibit purine nucleotide synthesis and are used in lupus, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and other conditions, including transplant. The major adverse effects of these compounds are GI intolerance, alopecia, and bone marrow suppression with

cytopenias, a risk increased with concomitant administration with allopurinol. A genetic test for thiopurine methyl transferase (the enzyme that metabolizes these compounds) is now available and should be performed in any patients considered for this agent [38].

Leflunomide

Leflunomide (Arava; Sanofi-Aventis, Bridgewater, NJ) is used for rheumatoid arthritis. This agent blocks pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase with decreased T-cell function. One group reported that an analogue inhibits mast cell mediator release in mice [39], and another group recently reported that leflunomide induces mast cell apoptosis [40•]. Administered orally at 10 or 20 mg daily, the major toxicities are GI intolerance, alopecia, potentially significant liver function test abnormalities, and concerns of possible interstitial lung disease. This agent is teratogenic with a tissue half-life of months to years, thus requiring a special washout with cholestyramine if conception is considered. To date, there are no reports for this drug in CU.

Abatacept

Abatacept (Orencia; Bristol-Myers Squibb, Princeton, NJ) is the first available agent that specifically blocks the interaction between antigen-presenting cells and T cells in a process of costimulation through the CD28 receptor expressed on the T cell [41••]. Unless a T cell receives a “second signal” through this receptor in conjunction with antigen presented through the T-cell receptor, the T cell will undergo one of two fates: anergy or apoptosis. In autoimmune diseases, this costimulatory step is important in initiating T-cell activation. Abatacept is a fusion molecule of the extracellular domain of cytotoxic T-lymphocyte antigen 4 (CTLA-4 [CD152]), which binds CD28 with high affinity (thus blocking the costimulatory signal), fused with the Fc portion of IgG1. It is intravenously administered monthly, is approved for rheumatoid arthritis, is being studied in lupus, and has been effective in psoriasis. Like other T-cell agents, its major side effects include an increased risk of infection. Belatacept, another costimulatory agent, is being studied in transplant and appears to be a more potent immunosuppressant than abatacept. Neither has been evaluated in CU.

Alefacept

Alefacept (Amevive; Astellas Pharma US, Deerfield, IL) is another agent active against T cells and is approved for psoriasis. It is a fusion construct of leukocyte function-associated antigen 3 (LFA-3 [CD58]) with the Fc portion of IgG1 that blocks the second signal of T-cell activation mediated through CD-2. In addition to effects on T cells, a recent study demonstrated coordinate reduction in antigen-presenting dendritic cells [42]. This agent is

administered by intravenous or intramuscular injection every 2 weeks for up to 12 weeks, and was studied in psoriatic arthritis in combination with methotrexate. Although effective in psoriasis, peripheral CD4 T-cell depletion and increased infection were noted. This agent has not been investigated in CU.

B-cell and antibody-directed therapies

The importance of B cells in the pathogenesis of many autoimmune diseases is increasingly recognized. Although one role of B cells is differentiation to terminal antibody-producing plasma cells, B cells are also recognized as efficient antigen-presenting cells and costimulatory cells for T cells; moreover, B cells themselves produce several cytokines, including TNF, IL-6, and IL-10 [43•].

Several therapies directed against B cells have been studied in autoimmune diseases. Rituximab (Rituxan; Genentech, South San Francisco, CA; and MabThera; Roche, Nutley, NJ) is a chimeric monoclonal antibody targeting the CD-20 molecule on the surface of maturing B cells, but not stem cells or plasma cells; it was originally developed for non-Hodgkin's lymphoma. It causes rapid and sustained reduction in peripheral B cells that may persist for more than a year. This agent is now approved for rheumatoid arthritis and is being studied in other autoimmune diseases [43•,44]. Recently, rituximab was shown to be effective in treating pemphigus and in a small number of patients with atopic dermatitis in an open-label study [45•]. There is a single case report of rituximab for CU in which the agent was not effective [46]. However, using this drug in CU requires careful consideration because of infusion-related reactions (eg, urticaria, angioedema, and anaphylactoid reactions) occurring in up to 30% of those treated. We are currently conducting a safety study using rituximab for CU as part of an investigator-held Investigational New Drug, which is currently on a US Food and Drug Administration–mandated clinical hold due to safety concerns in other diseases. In clinical trials, infections are increased with rituximab. Although immunoglobulin levels are only slightly decreased with a first course of therapy, there are indications that repeated administration decreases IgM and IgG [47••].

Other B-cell-directed therapies are in development, including additional monoclonal antibodies directed against CD20, ofatumumab, ocrelizumab, and a small molecule inhibitory protein (TRU-015) [43•]. Like rituximab, these agents cause rapid sustained decreases in peripheral B cells and have shown early efficacy in rheumatoid arthritis. Epratuzumab, another agent targeting the B-cell surface molecule CD22, is being studied in lupus. Several compounds that block B-cell proliferation through BlyS (B-lymphocyte stimulator) and APRIL (A proliferation-inducing ligand) are under investigation: belimumab, a monoclonal antibody directed against BlyS; briobacept, a fusion construct of BR3 (BlyS Receptor 3, CD268) with the Fc portion of IgG that binds BlyS; and

atacept, a soluble fusion construct of TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) with the Fc portion of IgG that binds BLyS and APRIL. These compounds decrease B-cell numbers, immunoglobulins, and autoantibodies.

Omalizumab (Xolair; Genentech, South San Francisco, CA, and Novartis, Annandale, NJ)—a human monoclonal antibody directed against IgE—is approved for moderate to severe persistent asthma. Several cases have been reported using omalizumab in various CU types. The first was a 12-year-old patient with cold-induced urticaria and elevated IgE level [48•]. Recent case reports include a 25-year-old patient with isolated cholinergic urticaria [49], and a small case series of three patients with refractory angioedema without urticaria [50•]. Two patients in the latter series had elevated IgE levels and the third had severe asthma; one also had sarcoidosis. A second case series of three patients with CU treated with omalizumab was recently reported [51]. Two patients had elevated IgE and two had anti-FcεRI antibodies. All had clearing of urticaria within a few days to weeks with omalizumab, 300 to 375 mg, every 2 weeks. The independence of clinical responses from IgE levels suggests non-IgE-mediated effects of the drug through T cells [52•] or receptor downregulation. A small randomized placebo-controlled trial has been completed of omalizumab in CU with encouraging results thus far (presented at American Academy of Allergy, Asthma, and Immunology, 2008, S. Saini, personal communication).

Neutrophil-directed therapies

Neutrophils are frequently seen in urticarial lesions, even without vasculitis. Neutrophils are important effector cells of inflammation and release leukotriene B₄, prostaglandin E₂, and proteases. Drugs including colchicine and dapsone that affect neutrophils have been used in CU. Colchicine has been used for gout for many years and in mild cases of cutaneous vasculitis and Behçet's syndrome, and is reported in treatment algorithms for CU. Published literature is sparse concerning its efficacy in urticaria. Dapsone is used for leprosy and is effective in several neutrophilic dermatoses and lupus skin disease. The drug inhibits lysosomal enzymes, myeloperoxidase function, neutrophil adhesion, and prostaglandin and leukotriene release. In an open-label study of 11 patients with CU who were treated with dapsone, 25 mg/d, all showed improvement [53]. In a more recent study, 65 patients with CU were randomized to dapsone, 50 mg/d, with antihistamines, or antihistamines alone for 3 months; however, this study was not blinded [54]. Although urticaria severity was reduced at 3 months compared with baseline in both groups, there was no difference between the two groups. Before using dapsone, it is critical to screen for glucose-6-phosphate dehydrogenase (G6PD) deficiency and to monitor for hemolysis even in patients with normal G6PD levels.

Mast cell and basophil targeting

The terminal effector cells responsible for urticaria symptoms are histamine-releasing mast cells and basophils. Several intrinsic abnormalities in their signaling pathways are recognized in patients with CU. Therapies directed specifically toward these cells have been limited, but as discussed previously, several drugs may affect them, including omalizumab, cyclosporine and tacrolimus, and hydroxychloroquine. Another agent currently used for chronic myelogenous leukemia and gastric stromal cell tumors, imatinib (Gleevec/Glivec; Novartis, Annandale, NJ), targets the protooncogene *c-abl* but also inhibits *c-kit*, the membrane receptor for stem cell factor expressed on mast cells. More recently, imatinib has been shown to recognize a mutated platelet-derived growth factor-α receptor or fusion with FIP1-like-1 (FIP1L1) responsible for many cases of hypereosinophilic syndrome [55•]. Imatinib also causes tissue mast cell apoptosis [56]. This agent is associated with severe edema, pleural effusions, myelosuppression, and GI side effects and has not been studied in urticaria.

Eosinophil-directed therapies

Variable numbers of eosinophils are present in urticarial lesions. However, many patients show no increase in eosinophils either in tissue or peripheral blood. Mepolizumab (Bosatria; GlaxoSmithKline, Philadelphia, PA), a humanized antibody to IL-5, has been effective for hypereosinophilic disease [57••]. However, mepolizumab did not lead to significant improvements in asthma or atopic dermatitis, despite a reduction in peripheral eosinophil counts. These studies suggest that anti-IL-5 therapy may be efficacious in diseases in which the eosinophil is the primary effector; however, its utility may be more limited in a complex disease (eg, asthma, atopic dermatitis, or CU) in which the eosinophil is but one of many inflammatory cells.

Cytokine antagonists

The inhibition of proinflammatory cytokines has proven to be an effective treatment for several inflammatory diseases. TNF is a pivotal cytokine in many Th1-mediated processes. Three TNF inhibitors are currently approved for rheumatoid arthritis: etanercept (Enbrel; Immunex, Thousand Oaks, CA), infliximab (Remicade; Centocor, Malvern, PA), and adalimumab (Humira; Abbott, Abbott Park, IL). Two additional agents are in the later stages of clinical development: certolizumab pegol and golimumab. Etanercept is a p75-TNF receptor fusion construct with the Fc portion of IgG, whereas adalimumab, infliximab, and golimumab are monoclonal antibodies. Certolizumab is an antigen-binding domain of an immunoglobulin (Fab') bound with polyethylene glycol to increase half-life. These agents have shown efficacy across a range of diseases: rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, Crohn's disease and

ulcerative colitis, and other conditions including uveitis, sarcoidosis, and even asthma. A role for TNF in urticaria has not been proven; however, TNF is a potent activator of endothelial cells, upregulates adhesion molecules, and increases cell trafficking to inflamed sites. One case has been reported using etanercept and infliximab in a patient with delayed pressure urticaria and concomitant psoriasis; improvement was noted immediately after therapy, thus allowing antihistamine discontinuation [58]. With more than 10 years' experience, the toxicities of TNF antagonists are well established. The risk of bacterial infection is similarly increased with all agents. Reactivation of latent tuberculosis and other granulomatous conditions is a significant concern, mandating purified protein derivative (PPD [tuberculin]) screening. There are concerns about using these drugs in patients with multiple sclerosis or demyelinating disease and congestive heart failure.

IL-1 has been implicated in some inflammatory diseases. Anakinra (Kineret; Amgen, Thousand Oaks, CA) is a recombinant IL-1-receptor antagonist approved for rheumatoid arthritis and dramatically effective in neonatal-onset multisystem inflammatory diseases including familial cold auto-inflammatory syndrome and Muckle-Wells syndrome, in which urticaria-like skin lesions may be present [59••]. Another agent, rilonacept (Arcalyst; Regeneron, Tarrytown, NY), recently received approval for cryopyrin-associated periodic syndromes. Rilonacept is an IL-1 antagonist that is a fusion construct of the IL-1 receptor and its accessory protein with the Fc portion of IgG. An inhibitor of IL-6, tocilizumab (Actemra; Roche, Nutley, NJ), is in the final stages of evaluation for approval in rheumatoid arthritis [60,61]. This monoclonal antibody, which is administered intravenously every 4 weeks, is directed to the gp130 component of the IL-6 receptor. IL-6 has several immunologic actions, including stimulating B-cell antibody production and driving the acute phase response. Side effects associated with tocilizumab have included infection, increased liver enzymes, and increased cholesterol.

Other immunomodulatory therapies

For many years, sulfasalazine (Azulfidine; Pfizer, New York, NY) has been used for ulcerative colitis and rheumatoid arthritis. The molecule is sulfapyridine linked covalently to 5-aminosalicylic acid. Its mechanisms of action are still unclear, but it decreases neutrophil respiratory burst, decreases immunoglobulin synthesis, impairs B-cell differentiation, affects T cells, and inhibits cytokine production. Several reports exist of sulfasalazine's efficacy in CU. A recent retrospective series reported 19 patients treated with an average sulfasalazine dose of 2000 mg/d [62•]. Improvements were noted in 74% of patients; however, 37% had a drug-related adverse event, including GI complaints, leukopenia, and transaminitis. Because this is a sulfa agent, it is contraindicated in patients with sulfa allergy. Hemolysis may be increased in patients with G6PD deficiency, and such patients should be monitored.

Methotrexate is another immunomodulatory therapy used in several IMIDs. Its primary mechanism of action at the doses used in these conditions is likely from release of anti-inflammatory adenosine rather than folate depletion [63]. Published data are limited on methotrexate in patients with CU. Two patients with recalcitrant disease were treated with 15 to 20 mg/wk; while on the medication, background medications were reduced and symptoms improved [64]. A recent letter reported limited details about 45 patients treated with methotrexate, 10 mg/wk, with apparent improvements [65]. Guidelines for the administration of methotrexate in autoimmune disease have been published [66]. All patients should receive supplemental folic acid, at least 5 mg/wk, and should be screened for hepatitis B and hepatitis C. Alcohol intake significantly increases the risk of hepatotoxicity and should be limited. All patients should be monitored for liver function and blood counts; the dose should be adjusted for renal insufficiency. Other common side effects include fatigue, oral ulcers, alopecia, nausea, and headache.

Endothelial activation and cell recruitment

The urticarial lesion is associated with the influx of inflammatory cells including neutrophils, eosinophils, lymphocytes, mononuclear cells, mast cells, and basophils. Activation of the endothelium has been demonstrated, with increased expression of adhesion molecules. Two inhibitors of cell adhesion have been used in other IMIDs. Natalizumab (Tysabri; Biogen, Cambridge, MA) is a monoclonal antibody directed toward the α -4 integrin, which is important in leukocyte recruitment to inflamed sites. The drug has considerable efficacy in multiple sclerosis and is approved in Crohn's disease [67,68]. The drug is efficacious, but the occurrence of progressive multifocal leukoencephalopathy has been concerning, and suggests a potential role for the α -4 integrin in protection against latent viral infection in the central nervous system [69•]. Efalizumab (Raptiva; Genentech, South San Francisco, CA) is a monoclonal antibody that binds CD11a integrin, also important in T-cell trafficking to inflamed sites. CD11a is involved in second signaling to T cells via leukocyte function-associated antigen 1 (LFA-1). The drug is currently approved for psoriasis. Although efficacious, a prompt and severe flare occurs upon drug discontinuation in some patients, suggesting that its effects are only static and do not change the fundamental course of the psoriatic process.

Conclusions

Although CU remains a challenge to treat, viewing it as an IMID—in terms of cells, cytokines, and other mediators—provides novel opportunities to pursue immunomodulatory therapy.

One difficulty in providing treatment guidance for severe CU is the lack of double-blind, randomized controlled trials, which are considered the best evidence of efficacy. Many immunomodulatory drugs are used and referred to

in treatment guidelines, but with the exception of antihistamines and leukotriene antagonists, evidence for their efficacy is mostly limited to case reports, small case series, and open-label experiences. The best available evidence with randomized double-blind studies is for cyclosporine, a drug with considerable toxicity. One reason for the paucity of larger controlled studies is the lack of a clear roadmap for clinical trial design and standardized outcomes in CU. Such barriers can be partially overcome by developing networks of investigators in clinical practice and in academic centers, who together can build a framework for studying this disease. Such consortia would allow patient referral for specific protocols in which drugs can be administered carefully, with observation for toxicities (eg, injection or infusion reactions, infection), and incorporation of studies that evaluate disease mechanisms in the context of targeted immunomodulation. Developing such networks offers the potential for opening additional avenues for funding clinical studies. Pharmaceutical companies are encouraged to provide funding to evaluate CU in larger studies that can more definitively evaluate efficacy.

This review has only briefly discussed some of the issues concerning toxicities of immunomodulatory therapy. Published guidelines for traditional immunomodulators outline appropriate screening, evaluation, and monitoring; however, these lists are constantly expanding as new agents are approved [70••]. Before prescribing immunomodulatory therapy, practitioners are encouraged to consult with subspecialists who routinely use these medications to understand the potential adverse effects so that proper information (or informed consent) can be provided to patients before embarking on what may be a promising but potentially risky therapy.

The treatment of other autoimmune diseases with targeted immunomodulatory therapy has provided clinical responses hitherto unseen. Rheumatologists now speak of "remission" as an achievable goal for many patients with rheumatoid arthritis, and are developing studies that evaluate maintenance of remission in the absence of treatment. With all indications pointing to urticaria as a similarly mediated complex IMID, we can look forward to a future in which lasting remission can be discussed for this condition. The currently available and newly emerging therapeutics offer tremendous promise to fill an unmet need for patients with CU, many of whom are steroid dependent or significantly impaired by their condition. It is hoped that understanding the disease in an IMID context will facilitate patient, provider, and payor understanding of the need for more aggressive therapies beyond terminal mediator blockade.

Disclosure

Dr. Bingham reports grant and/or research support from Amgen, Abbott, the Arthritis Foundation, Bristol-Myers-Squibb, Genentech, the US National Institutes of Health, Procter and Gamble, and Wyeth. He has served as a consultant to Abbott, Amgen, Genentech, Novartis, Targeted Genetics, and UCB.

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