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Chronic Spontaneous Urticaria and Omalizumab as an Emerging Therapy

Review Article

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Abstract

Chronic spontaneous urticaria (CSU) is a debilitating condition that affects individuals for an extended period of time. Chronic urticaria is characterized by the presence of characteristic wheal and flare lesions for greater than six weeks. This inflammatory reaction is primarily mediated by histamine release from mast cell degranulation although multiple other physiologic factors are involved. CSU is a diagnosis of exclusion where definitive triggers are not identified, however, associations with autoimmune conditions have been investigated. Second-generation antihistamines are the recommended primary treatment for CSU, but a significant number of cases are refractory to conventional treatments. Omalizumab (Xolair) is an anti-IgE biologic agent recently approved by the Federal Drug Administration for the treatment of CSU. Studies have shown favourable safety profiles and efficacy. Omalizumab shows promise as an agent for the management of recalcitrant symptoms and overall improvement of quality of life.

Keywords: Urticaria; Omalizumab; Xolair; Biologics; Pruritus.

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Definition

Chronic spontaneous or idiopathic urticaria (hereafter referred to as CSU) is a condition that can significantly affect an individual's quality of life. CSU can impair an individual's functional abilities, sleep patterns, and esteem, affecting quality of life to an extent comparable to heart disease [1-5]. Urticaria is characterized by wheals that arise and wane by the end of a 24-hour period. Although lesions may resolve quickly, new wheals may also form resulting in the chronicity of the condition. Chronicity is formally defined with the presence of these lesions for more than six weeks duration [6,7]. Acute urticaria, conversely, resolves in less than six weeks. Forms of chronic urticaria other than CSU involve known triggers, such as delayed pressure, cholinergic, and other physical triggers [8,9]. CSU, however, usually does not have a known etiology and is a diagnosis of exclusion. It is unlikely to find the precipitating agent in most cases [10].

Epidemiology

CSU is seen in approximately 0.5% of the general population and has a female preponderance [11-14]. Angioedema or urticaria can affect up to 20% of individuals within their lifetime. Although people of any age can be affected, there is a peak age of incidence in the range of 20-40 years of age [15]. Other factors such as race, sex, occupational exposure, geography, and season may increase exposure to agents that may trigger urticaria [16]. Considering all types of chronic urticaria, up to 90% of cases have an unknown cause and are labelled CSU [17].

Etiology, Pathophysiology, and Clinical Presentation

The natural history of CSU usually involves spontaneous resolution with symptomatic clearance occurring in 50% within one year, 65% within three years, and 85% within 5 years. Fewer than 5% of cases will persist for greater than ten years [16,18].

The underlying pathophysiology of urticaria involves swelling, wheal formation, and erythema due to increased capillary permeability and vasodilation predominantly mediated by histamine released from mast cells [19]. Histamine mainly acts on H_1 histamine receptors, but also stimulates H_2 histamine receptors to a lesser extent [16]. Leukotrienes, cytokines, and chemokines are also involved with increased cellularity and inflammation [16,20]. Pruritus is associated with histamine-stimulated afferent type C fibers and substance P release [16]. Urticaria usually involves inflammation and increased vascular permeability in the more superficial papillary and mid-dermal layers while swelling in the

deeper reticular dermis and subcutaneous or submucosal tissue is implicated in angioedema [21]. Acute urticaria is normally associated with mast cell degranulation due to IgE-antigen cross-linking [19]. Chronic urticarias, including CSU, may involve mast cell stimulation via anaphylotoxins C3a and C5a from complement activation, anti-IgE receptor antibodies, and anti-IgE antibodies [22,23]. A combination of a lower threshold for mast cell activation and levels of physiologic compounds such as substance P, endorphins, enkephalins, gastrin, vasoactive peptide, and somatostatin may also play a relevant role [19,24-26].

Coagulation is also associated with the cascade of events involved in urticaria due to the reciprocal activation of inflammation and clot formation systems. Patients with active urticarial episodes display increased levels of coagulation biomarkers which may return to normal levels upon remission. Notable coagulation markers include prothrombin fragment F1+2, activated factor VII, and D-dimer. Eosinophils and mast cells may serve as linking points between the inflammatory and coagulation components of urticaria. Activated eosinophils express tissue factor which activates factor VII and produces thrombin. Experimentally, thrombin has been shown to interact with the protease-activated receptors of mast cells leading to degranulation suggesting that abnormal coagulation may also contribute to urticaria [27,28].

The etiology of CSU and the causes that precipitate urticarial exacerbations have remained elusive. Clinical correlations of a higher incidence of Helicobacter pylori in those with CSU has been observed, but a definitive causative role is still under investigation [29-31]. The contributions of other infectious agents, such as those causing hepatitis, are also being studied [32]. Increasingly, studies have found a link between autoimmunity and CSU [4,8,13,16]. Thyroid disease can be regarded as a marker of autoimmunity due to its association with conditions such as type I diabetes mellitus, pernicious anemia, and systemic lupus erythematosus [17,33]. Furthermore, rheumatoid arthritis is more prevalent in patients afflicted with both hypothyroidism and CSU and rheumatoid factor is elevated in CSU patients [34,35]. This relationship between autoimmunity and CSU has mostly been explored in the context of thyroid disease, although most patients are euthyroid. The onset of CSU is 16 times greater in those that demonstrate thyroid autoimmunity in comparison to those without thyroid autoimmunity [36]. Within a study, patients with CSU were seen to have antithyroid antibodies in 27.3% of cases, but no autoantibodies were observed in the control group. These antibodies included anti-thyroglobulin, anti-thyroid stimulating hormone, and anti-thyroperoxidase immunoglobulins [17]. A definite causative relationship between CSU and thyroid autoimmunity has not been elucidated, but it is postulated that exacerbations may be due to thyroperoxidase binding to complement protein C4 and activating the complement cascade via the classical pathway. Indeed, elevated levels of C4 have been observed in Hashimoto's thyroiditis [37]. Complement proteins can also bind mast cells and lead to degranulation [19,23]. In addition, treatment of thyroid disease has been linked with the remission of CSU episodes and decreased C4a levels [38]. An increased incidence the development of angioedema is also seen in those with both autoimmunity and CSU. Indeed, it has been hypothesized that thyroid disease and CSU coexist as a result from a patient's increased propensity to develop autoimmune conditions and that thyroid disease can lead to exacerbations [4].

Other aspects of autoimmunity may also be involved in CSU. In addition to antithyroid antibodies, anti-FcεRI and anti-IgE autoantibodies have been associated with CSU in 40% and 10% of cases, respectively. The postulated mechanism of action of these autoantibodies involves basophil and mast cell degranulation via complement and C5a release [17,39]. These autoantibodies have also been associated with more severe CSU episodes, but do not necessarily correlate with increased resistance to therapy or a more complex disease course [33,40].

Various investigative measures are also conducted to determine autoimmunity in patients with CSU. The autologous skin test is usually used as a sign of autoimmune anti-IgE receptor antibody. The procedure involves the injection of a patient's own serum into their skin and observing if there is a wheal and flare reaction. Although this bolsters the correlation between CSU and autoimmunity, the test is not completely sensitive since not all patients with positive autologous skin tests are found to have anti-IgE receptor antibodies [41,42].

In addition to laboratory tests for indicators of auto-antibodies and autoimmunity, investigation of CSU involves the examination of patient history and other tests to exclude other possible precipitants. Investigative measures include a complete blood count, erythrocyte sedimentation rate, C reactive protein measurement, and skin biopsy. CSU is diagnosed when the clinical picture is congruent with chronic urticaria, but other potential causes have been excluded [43,44].

Treatment

Treatments for CSU largely focus on symptom control until the condition remits. Many treatment guidelines have covered this subject matter and a novel biologic agent, omalizumab (Xolair), is being evaluated and utilized in the context of CSU [43,45-48].

In terms of prevention and control, food and diet may have a role in affecting CSU activity. Exclusion of pseudoallergens from a diet in those with CSU may benefit certain patients, but this relationship may need further investigation [49].

Second-generation antihistamines are considered first-line therapy to control the symptoms associated with CSU and also tend to be less sedating than first-generation agents. In addition to this, non-pharmacologic measures involve avoidance of agents known to trigger or exacerbate episodes, but dietary changes are not always recommended [46]. The dose of the second-generation antihistamine can be increased to up to four times the standard dose if the symptoms are recalcitrant. If there is inadequate symptomatic control with second-generation antihistamine monotherapy, other agents can be utilized in addition [50,51]. This can involve the additional administration of an H_2 antihistamine receptor antagonist, or leukotriene receptor antagonist. First-generation antihistamines can also be used, but are usually taken at bedtime to minimize functional interference due to sedative effects [52,53]. The belief that sedating first-generation antihistamines enhance sleep, however, was recently contested in a study whose findings lend support to monotherapy with second generation antihistamines [54]. One or more of the mentioned alterations can be implemented to achieve symptom control. Finally, different agents have been utilized for refractory CSU. Cyclosporine has been used for recalcitrant CSU and can induce remission, but the potential ad-

verse effects need to be considered. The anti-inflammatory agents dapsone, sulfasalazine, hydroxychloroquine, and colchicine have also been used, but evidence of their efficacy and safety is limited [46].

Systemic corticosteroids are also used for refractory CSU as rescue therapy, but faster relief from symptoms is not necessarily seen when used in conjunction with antihistamines [55]. Episodes and exacerbations of symptoms may be treated with systemic corticosteroids in the short-term until other agents provide relief and control, but long-term use should be avoided if possible due to the long-term adverse effects [56,57].

Omalizumab is a humanized monoclonal antibody that has been approved for the treatment of recalcitrant chronic urticaria. The biologic agent was originally indicated for those with refractory allergic asthma [58,59]. Omalizumab is an anti-IgE antibody which forms immune complexes to free IgE. As a result, decreased IgE-mediated mast cell and basophil degranulation and histamine release would occur, reducing the cascade of events involved in urticaria. This is thought to reduce IgE binding to mast cells and may result in FcεRI and FcεRII receptor down-regulation [60]. Other experiments have found that omalizumab decreases levels of IL-31, a putative dermal pruritogen, in those treated for CSU [61]. Although antihistamines are the main therapy used for urticaria, numerous studies have seen that many patients are still symptomatic with unresolved CSU, which may respond to omalizumab [5,50,62,63]. Preliminary studies have been conducted regarding its efficacy and safety in patients with chronic urticaria and the findings have generally found a low incidence of adverse effects [64-75]. Clinical experience with urticaria has shown that it is an agent that leads to swift symptomatic control and remission. Varied treatment regimen may be needed to tailor individual treatment plans and can involve longer term therapy with higher doses [76]. Recently, phase three trials of omalizumab used in the treatment of CSU have reported favourable findings with positive response and symptomatic control in patients with refractory episodes. Overall, omalizumab has been observed to have a similar safety profile to placebo [77-79].

The use of omalizumab has been approved by the Federal Drug Administration at 150 mg and 300 mg in order to treat candidates aged 12 or older that have not achieved a sufficient response from antihistamine therapy [46]. The dose is usually dependent on the clinical response to treatment rather than patient weight [80]. Omalizumab's mechanism of action may involve a reduction in the level of free IgE and its FcεRI receptor, decreasing mast cell and basophil stimulation and inflammatory mediator release. This claim has been supported by decreased late phase reaction inflammation and smaller wheal formation following omalizumab administration, but is still under investigation [81-83]. In addition to treating patients with CSU resistant to conventional antihistamine therapy and few adverse effects, omalizumab is also able to provide relatively rapid relief even upon retreatment [84,85]. The duration of remission, however, is still variable among patients [84].

Studies relating to the safety of omalizumab used for allergic asthma found the drug risk profile to be favourable, with no definitive evidence to support the development of anti-omalizumab antibodies, increased incidence of malignancy, or thrombocytopenia during treatment [86,87]. Although adverse events are uncommon, desensitization to omalizumab, urticaria, injection-site reactions, serum sickness, and anaphylaxis have been reported following omalizumab administration [88-92].

Omalizumab seems to show promise in adding to the arsenal for the treatment of refractory CSU. Although omalizumab has not been universally adopted and studies are still being conducted, favourable efficacy and safety profiles show promise for widespread use. In addition, other biologic agents may also be used for the treatment of refractory CSU in the future, such as rituximab [93-95]. Given the number of cases of recalcitrant CSU, other alternative therapies need to also be considered when patients do not respond to omalizumab. Despite this caveat, omalizumab is able to assist and provide control to refractory CSU.

CSU can be a frustrating and debilitating disease due to its unpredictability with exacerbations, variable duration, and lack of symptom control in some patients. The advent of new treatments with favourable safety profiles allows for the aggressive treatment of CSU without the increased concern for adverse effects. Developments that help further manage the condition and improve quality of life are imperative and can provide significant relief to those afflicted with CSU.

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