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Chronic Idiopathic Urticaria: Treatment with Omalizumab

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ABSTRACT

Chronic idiopathic urticaria (CIU) is a common autoimmune skin condition characterized by spontaneously recurring hives for 6 weeks or longer. The new terminology used for CIU in most countries including Canada is chronic spontaneous urticaria (CSU). CSU is associated with significant psychosocial morbidity with a markedly negative impact on overall quality of life. Conventional approaches with antihistamines, even at high doses, is effective in about 50% of patients suffering from CSU. A new treatment option, omalizumab, a humanized monoclonal antibody against the Fc domain of IgE, has undergone the scrutiny of randomized research studies evaluating the efficacy in CSU. This editorial reviews mechanisms of action of omalizumab, efficacy, cost and potential side effect profile. Omalizumab has emerged as a very promising treatment option for patients with CSU. Future research is necessary to establish standardized protocols related to dosing as well as monitoring possible adverse effects of long-term treatment.

Key Words: angioedema, antibodies, anti-allergic agents, autoimmune skin disorder, hives, hypersensitivity, immunoglobulin E, monoclonal antibody, omalizumab, urticaria, Xolair

Introduction

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is a common autoimmune skin disease characterized by spontaneously recurring hives or welts, which may also be accompanied by deeper cutaneous swelling termed angioedema. The primary symptom causing significant disability is itchiness or pruritus.¹ The diagnosis is defined as urticarial skin lesions occurring intermittently or continuously for more than 6 weeks. A fairly

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common condition, urticaria occurs across all age groups and has a lifetime prevalence of about 20% with about 1% of the population suffering from the chronic form.² CSU occurs largely in young women between 20 and 40 years age.^{3,4} Notably, 70% of patients diagnosed with CSU report symptoms lasting more than 1 year and a significant 14% report non-remitting symptoms which have lasted for more than 5 years.⁵ This condition has been associated with significant psychosocial impairment; specifically impacting emotional and physical health-related quality of life indices; resulting in substantial disability and diminished productivity.⁶⁻⁸ Notably, the negative impact on quality of life measures reported by patients with CSU is on par with the severity reported by patients with triple vessel ischemic coronary disease. Specifically, patients in both clinical populations report similar levels of emotional distress, social isolation and lethargy.^{9,10}



[Treatment of Chronic Spontaneous Urticaria](#)

Current practice guidelines for management of CSU describe a stepwise approach with non-sedating H1 oral antihistamines as the initial agents, these can be given in up to four times the FDA recommended dose.¹¹ However, close to half of all CSU patients do not achieve adequate symptom relief with H1 antihistamines alone.¹² Second-line therapies can involve addition of H2 blockers although these are not recommended as first, second or third-line treatment because of low evidence supporting their clinical efficacy. The H2 blocking agents and anti-leukotriene medications are often tried because of their excellent safety profiles. If remission is not induced, third-line treatments may be initiated; this includes use of immune modulators. To date, cyclosporine has been the best studied agent with demonstrated efficacy based on adequately powered studies of good quality. Its significant toxicity profile, however, has limited its widespread use in many patients, especially in the older population dealing with other comorbidities.¹¹ Other immune modulators which have been used in refractory CSU include tacrolimus, mycophenolate mofetil, hydroxychloroquine, sulfasalazine and even intravenous immunoglobulin. In addition to the limited data supporting use of these agents in managing CSU, many of them are associated with substantial and often unacceptable toxicities. Systemic glucocorticoids have also been used in refractory cases and while consensus guidelines recommend their use to be limited to exacerbations, clinical practice has often necessitated their longterm use in many patients, again posing less than desirable side effects.¹³

Treating CSU is challenging, as there are often no identifiable indicators as to the responders to specific treatments. Cutaneous mast cell degranulation with release of histamine and other mediators are ascribed to urticaria, however, nonimmunoglobulin E (IgE) and non-immunologic mast cell activation is responsible for ongoing urticaria.¹⁴ In up to 50% of patients with CSU, an autoimmune mechanism is thought to mediate the disease process; this either involves autoantibodies to the alpha chain of the high affinity IgE receptor or intrinsic IgE immune modulation is believed to account for the pathophysiology.^{15,16} Research-based assays have been developed to isolate an autoimmune etiology; however, at the present time, these are not readily available nor practical in a clinical setting.¹⁷

[Omalizumab: Mechanism of Action](#)

In the last few years, there has been a burgeoning interest in expanding the use of omalizumab beyond its originally approved use as adjunctive therapy for

refractory asthma to CSU. Recently approved in Canada for CSU management, omalizumab is a fully humanized recombinant monoclonal antibody which binds to the fragment crystallizable (Fc) region of the IgE molecule which itself binds to FcεRI.^{18,19} In theory, this structure precludes anaphylactogenic potential since the drug does not interact directly with IgE, which is already bound to cell surfaces. Therefore, mast cell or basophil degranulation would not be possible.^{20,21} Functionally, omalizumab binds to circulating IgE, irrespective of allergen specificity. This results in circulating IgE-anti-IgE complexes, which are biologically inert and have specifically been shown not to activate the complement system.^{19,20,22} Notably, reductions in circulating IgE reaching up to 99% have been reported in studies (that is free IgE not bound to omalizumab).^{22,23} Interestingly, these serologic changes are seen within the very first administrations of the drug and are typically maintained throughout the duration of treatment; although the precise doses in CSU have not yet been established. Omalizumab has also been shown to down regulate FcεRI on basophils,²⁴ mast cells,²⁵ and dendritic cells.²⁶ A reduction in the expression of FcεRI on basophils and mast cells decreases the binding of circulating IgE, thus preventing the release of inflammatory mediators. Although most CSU patients have no identifiable allergy triggers, and there is not necessarily an increased incidence of atopy or high IgE levels, chronic urticaria may develop due to many stimuli. These include NSAIDs use, certain foods and even emotional stress. Omalizumab has also been shown to reduce the expression of FcεRI on dendritic cells; thereby attenuating the degree of allergen presentation and processing.



Evaluation of Efficacy

In addition to initial observation studies, case reports^{27,28} and one proof-of-concept study²⁹, there have been four prospective randomized clinical trials which have directly evaluated the clinical efficacy of omalizumab in treatment of refractory CSU³⁰⁻³³, in addition to one multicenter double-blinded placebo-controlled study³⁰. Omalizumab has been evaluated using a total pool of approximately 1,000 CSU patients across all studies to date.²⁷⁻³² Results have demonstrated clinically significant efficacy of omalizumab in decreasing pruritus and Urticaria Activity Scores (UAS - a widely used patient-reported outcome measure for patients with CSU) in comparison with conventional treatments. Specifically, studies have demonstrated symptom attenuation and improvement on quality of life measures in adult patients treated with omalizumab for 6-20 months.^{27,34} In one study, which enrolled patients presenting with moderate to severe CSU who were unresponsive to antihistamines, omalizumab was associated with clinically relevant decreases in severity of hives and associated pruritus, as well as meaningful improvement on quality of life questionnaires.³² Notably, omalizumab often demonstrates an onset of action within 1 week of drug initiation, inducing complete remission; however, symptoms return when treatment is stopped, generally within 1 to 2 months. Also of relevance is the demonstrated efficacy of omalizumab in chronic inducible urticarial, such as cold and delayed pressure urticaria in small numbers of patients, for whom treatment options have generally been rather limited and outcomes unsatisfactory.³⁵

In real life studies omalizumab generally induces remissions in 50% of patients after the first dose.³⁵ Overall, more than 70% of patients achieve complete remission at some point within their treatment course. About 80% have a clinically significant response overall. The dose interval is generally between 4-8 weeks in most patients. More research is needed to more fully evaluate the dose interval and complete remission rate. The 300 mg dose was superior to

the 150 mg dose in randomized clinical trials.³²

Treatment Cost

Omalizumab is substantially more expensive than mainstream therapies that have been traditionally used to treat CSU. Despite its high cost at the present time, it can be argued that using omalizumab in selected patients with refractory and chronic urticaria may in fact defray the potential long-term financial costs associated with conventional therapies; in addition to alleviating the psychosocial burden associated with loss of productivity.



Side Effect Profile

Use of omalizumab in the asthmatic population is more extensive compared to CSU. In asthma there are reports of anaphylactic reactions in about 1 in 50,000 injections. It should be noted, however, that omalizumab is designed to interact with the Fc region of the IgE molecule, making its anaphylactogenic potential very low and clinical experience confirms that it is safe.^{20,21} There is still a recommendation for all patients to be observed for 2 hours after the first injection as well as carry epinephrine auto-injectors as some anaphylactic reactions have been reported as being delayed. Recently, the malignancy warning has been removed from the product monograph as patients with undiagnosed cancer were enrolled in one early trial.³⁴ The most common adverse side effects reported by patients include viral infections, headaches, sinus inflammation; however, these did not reach statistical significance when compared to patients enrolled in the placebo group. Notably, omalizumab is approved for children >12 years of age. The data available on its safety in children showed that after 1 year of use, there was a slight increase in frequency of headaches and upper respiratory tract infections in the omalizumab group compared to placebo.³⁶

Future Directions

Omalizumab has emerged in recent years as a very effective treatment for refractory CSU. Future research should aim at investigating its mechanism of action and optimal dose schedule and treatment duration required for long-term remission. To date, the longest trial duration has been 24 months.³⁷

Conclusion

Chronic spontaneous urticaria (CSU) or CIU is a common autoimmune skin condition characterized by spontaneously recurring hives, occurring either intermittently or continuously for 6 weeks or longer. A significant association is a deeper localized swelling called angioedema, which is observed in about one-third of patients.¹ This is associated with significant psychosocial morbidity in the form of depression, social isolation and lethargy.^{9,10} The impact of CSU on quality of life is notably substantial. There are recently developed standardized tools to assess the quality of life in CSU.³² A simple general test to assess disease severity is the Urticaria Activity Score (UAS7) that assesses pruritus and urticaria severity weekly, which should be used in clinical practice.³⁸ Conventional treatment guidelines prescribe a stepwise approach with non-sedating non-impairing antihistamines as first-line agents followed by increasing to four times the licensed doses as second-line treatment.² Thirdline treatments include cyclosporin, which is associated with toxicity and requires frequent monitoring.^{11,12} Omalizumab, a fully humanized monoclonal antibody against the Fc domain of IgE, has gained widespread use as a new third-line

treatment in CSU. A solid body of research including double-blinded, randomized clinical trials investigating its clinical utility in inducing remission in CSU has demonstrated robust efficacy.²⁷⁻³³ Specifically, patients treated with omalizumab experienced clinically relevant decrements in severity of hives and associated pruritus, as well as meaningful improvement on quality of life measures.³² Omalizumab often demonstrated onset of action within 1 week of drug initiation, although the treatment generally appears to be given every 4 to 6 weeks. Two doses of 150 mg and 300 mg have been shown to be effective. In such, omalizumab has emerged as a very promising treatment option for patients with CSU. Future research will need to establish standardized protocols related to dosing and duration, as well as monitor possible longterm side effects, particularly in vulnerable clinical populations.



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