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Chronic Refractory Idiopathic Urticaria

Indira Acharya[1], Ashik Pokharel[1], Ashbina Pokharel[2], Lanaya Williams Smith[3]

[1]Department of Internal Medicine, MedStar Union Memorial Hospital, Baltimore, Maryland, USA
[2]Department of Internal Medicine, William Beaumont Hospital, Royal Oak, Michigan, USA
[3]Department of Internal Medicine, MedStar Good Samaritan Hospital, Baltimore, Maryland, USA
Email: assanesall513@gmail.com

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Abstract

Background: Chronic spontaneous urticaria (CSU) is a complex medical condition characterized by substantial morbidity and a negative impact on one's quality of life. There are several treatment approaches available, tailored to the severity of the condition, which can enhance overall quality of life. **Aim:** In this article, we outline a systematic approach to managing chronic urticaria, while also elucidating the available treatment strategies for cases that prove resistant to conventional therapies. To illustrate our points, we present a clinical case as a practical example. **Case Presentation:** Here, we present a patient with CSU since childhood who presented in the context of refractory hives and generalized arthralgia that responded well to omalizumab therapy with no further relapse. **Conclusion:** Omalizumab is a biological agent that offers a potential treatment option for CSU. It is available for individuals twelve years and older who have not responded well to conventional treatments. It has demonstrated good efficacy with a relatively low rate of clinically significant adverse effects. Nonetheless, there is a dearth of research regarding the optimal method for tapering the dosage and determining the duration of treatment.

Keywords

Omalizumab, Biological Agent, Chronic Spontaneous Urticaria (CSU), Conventional Treatment, Relapse

1. Introduction

CSU, a rare skin disease driven by mast cells, manifests itself as recurring wheals, angioedema, or a combination of the two for more than six weeks [1]. The initial treatment approach involves the use of second-generation H1 antihistamines. If a patient does not exhibit a satisfactory response to this treatment, alternative options include escalating the dosage of second-generation H1 antihistamines,

incorporating H2 antihistamines, first-generation antihistamines, or leukotriene receptor antagonists (LTRAs). More than 50% of CSU patients do not respond to conventional antihistamine therapy [2]. In cases of refractory urticaria, the last resort may be the consideration of immunosuppressants or biologics [3]. Further research is needed to determine optimal treatment duration, as well as formulating correct methods for up titrating and tapering doses. We present a case in which a patient experienced worsening hives and did not respond adequately to Levoicetrizine, Hydroxyzine, and Prednisone. Ultimately, her condition was successfully managed with Omalizumab.

2. Case Presentation

A 40-year-old woman visited to a rheumatology office with progressively worsening hives throughout the body along with pain in multiple joints for one month, without notable factors exacerbating or reducing her symptoms.

Her medical history was notable for allergic rhinitis (with allergy blood testing positive for tree pollen), contact dermatitis from betadine and long-standing CSU that began at the age of ten years. She previously had monthly urticaria flares treated with second-generation antihistamines with some degree of relief. She also had a history of dry eyes and dry mouth however she denied any oral or nasal ulceration, angioedema, history of psoriasis or dental caries. One month ago, following a periodontal procedure, she was prescribed 7 days course of Amoxicillin which subsequently triggered a series of hives that spread throughout her body. These hives typically resolved completely within 6 to 24 hours and were accompanied by polyarthralgia. Since then, second-generation antihistamines have had little to no effect in providing further respite.

On presentation, the patient was afebrile, normotensive with preserved saturation and pulse rate. Physical examination showed erythematous, edematous and blanchable plaques throughout the body sparing the palm and soles. Additionally, there were scattered erythematous and edematous plaques with areas of confluence overlying the bilateral knees and wrists in association with tenderness to palpation. The distal interphalangeal joints of both hands had marked synovitis. Labs (**Table 1**) were notable for positive ANA but with no titer and no definite pattern, positive Ro 52 antibody and elevated complement C4 level. Lyme disease PCR, coxsackievirus antibody, IgE autoantibodies against thyroperoxidase (TPO) were negative and serum total IgE level was not elevated. In response to her reported intermittent epigastric pain, an esophagogastroduodenoscopy was conducted. This procedure was also intended to exclude the presence of *Helicobacter pylori* infection or parasitic infestation, both of which could serve as triggers for her urticaria symptoms. It revealed normal esophageal mucosa, with scattered redness in the antrum of the stomach, prompting the collection of a biopsy from that area. The biopsy result showed fragments of both oxyntic and mixed-type gastric mucosa with mild chronic gastritis, yet no signs of *Helicobacter pylori*, *Giardia trophozoites*, or any other distinct microorganisms on the mucosal surface.

Table 1. Laboratory diagnostics.

Parameters	Normal range	Result
ESR	0 - 20 mm/hr	61 mm/hr
CRP	0 - 3 mg/L	12.7 mg/L
Eosinophil	0.0% - 6.0%	1.9%
Total serum IgE level	150 - 300 UI/ml	170 UI/ml
Absolute eosinophil count	0.0 - 0.7 k/uL	0.1 k/uL
Anti-dsDNA IgG	<201 IU/mL	77 IU/mL
Anti-Smith IgG	<7 U/mL	1.5 U/mL
ANA IgG	<20 units	115. 88 units (nuclear and cytoplasmic patterns not observed)
Anti SSB/La IgG	<7 U/mL	0.8 U/mL
Anti-Ro 52 IgG	<20 CU	48.7 CU
Anti Ro 60 IgG	<20 CU	<4.9 CU
Anti-SCL 70 IgG B	<7 U/mL	<0.6 U/mL
Anticentromere protein B	<7 U/mL	0.5 U/mL
Anti-Jo1 IgG	<7 U/mL	0.8 U/mL
Anti-CCP IgG	<7 U/mL	1.7 U/mL
Complement C3	81 - 157 mg/dL	150.469 mg/dL
Complement C4	13 - 39 mg/dL	60.689 mg/dL
HLAB27 antibody	negative	negative
Creatinine	0.50 - 1.04 mg/dL	0.82 mg/dL

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Anti-ds DNA: anti double stranded DNA; ANA: antinuclear antibody; Anti SSB: anti-Sjogren's syndrome type B antibody.

The episodes of urticarial lesion and arthralgia following a course of Amoxicillin were concerning for serum sickness like reaction however in the absence of fever, lymphadenopathy and exposure to Amoxicillin more than one month ago, it was less likely. IgE mediated drug reaction with urticaria was of less concern as arthralgia is not common in this type of reaction and patient's serum IgE level was within normal range. Drug rash with eosinophilic and systemic symptoms (DRESS) was less likely as she did not have any fever and her eosinophil counts were not elevated. Stevens-Johnson syndrome was unlikely due to lack of sloughing of her skin. Drug induced cutaneous vasculitis was ruled out as lesions were non palpable, blanching, without residual hyperpigmented changes. Urticarial vasculitis was deemed unlikely in this case, given the rapid resolution of the plaque within a day without any lasting post-inflammatory hyperpigmentation. The diagnostic criteria for urticarial vasculitis consist of 2 major factors: urticaria lasting over 6 months and hypocomplementemia, as well as 2 minor criteria: any 2 of arthralgia, glomerulonephritis, ocular involvement, abdominal pain, suppressed C1q level, or dermal venulitis. In this instance, the patient fulfilled just 1 major criterion (urticaria lasting over 6 months) and 1 minor criterion (arthralgia). Given the absence of the necessary additional major criteria, a

skin biopsy was considered unnecessary. After excluding potential alternative diagnoses based on clinical symptoms and laboratory parameters, our diagnosis was chronic spontaneous urticaria.

The patient was asked to avoid Amoxicillin and continue taking levocetirizine 10 mg daily. However, given lack of response to levocetirizine, she was ultimately prescribed oral methylprednisolone at a daily dose of 4 mg for three weeks. While this provided some relief from her discomfort, she continued to experience daily hives. Patient's positive Ro 52 antibody was initially thought to be associated with systemic lupus erythematosus (SLE) and Sjogren syndrome however there was no evidence of objective markers for SLE like positive anti-dsDNA and anti-smith antibodies or low complement level and explicitly SSA/SSB antibodies were negative. She was initially started on hydroxychloroquine 200 mg twice daily along with levocetirizine 10 mg twice daily and hydroxyzine 25 mg nightly. As Ro 52 is often associated with interstitial lung disease, chest x-ray was also pursued that was unremarkable. She also visited an ophthalmologist who performed a Schirmer test that showed wetting of 8 mm on the strip after 5 minutes, suggesting slight dryness of bilateral eyes. As a result, she was started on restasis eyedrop.

In her 3 months follow-up, she continued to have persistent hives associated with itching, fatigueness and polyarthralgia though her eye symptoms improved. She was started on monthly omalizumab 150 mg subcutaneous injection and hydroxyzine on as needed basis. After receiving monthly omalizumab for 6 months, she had no further hives or outbreaks and her acute phase reactants returned to normal levels. She was switched to omalizumab injection once every 2 months and had a persistent clinical response in 6 months. Afterward, we planned to extend the interval by an additional month every six months and progressively decreasing the frequency of omalizumab administration until it reached once a year. Ultimately, our goal was to discontinue omalizumab once the patient achieved a clinically relapse-free state.

3. Discussion

Urticaria is a common skin condition with a prevalence of approximately 20% [3] in the general population and is characterized by pruritic wheals and flares of skin, with an occasional bout of angioedema [2]. It is classified as acute (for less than six weeks) or chronic (lasting more than six weeks). Chronic urticaria can be subdivided into two primary groups, depending on whether the symptoms arise spontaneously or are triggered by an identifiable stimulus (**Figure 1**) [4]. Identified causes include drugs, foods, infections (hepatitis B/C, Epstein-Barr virus, Herpes simplex, *Helicobacter pylori* and helminthic parasitic infections) and systemic conditions like cryoglobulinemia, serum sickness, SLE, juvenile rheumatoid arthritis, Sjögren syndrome, still disease, thyroid disease, and neoplasms (mainly lymphoreticular malignancy and lymphoproliferative disorders) [5] [6].

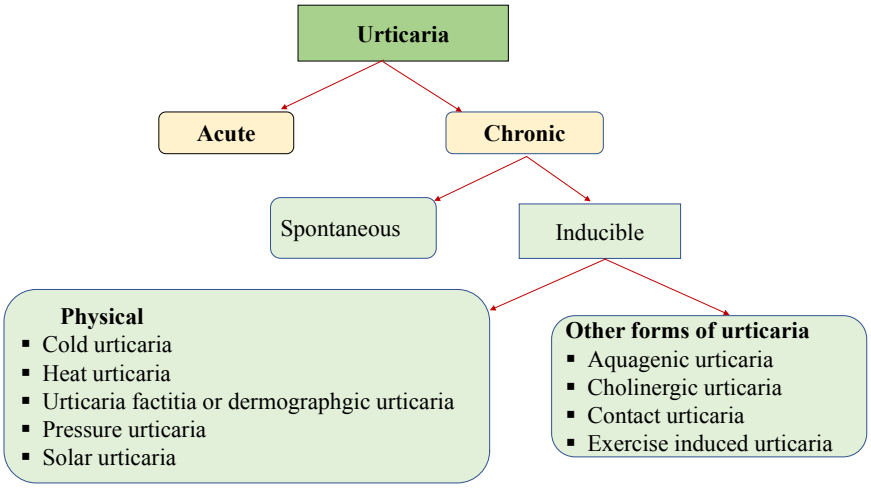

Figure 1. Classification of urticaria.

CSU, also called chronic idiopathic urticaria (CIU), is a complicated disorder that affects an estimated 1% - 2% of the global population and has a prolonged duration of average 1 to 5 years [7]. The severity of impairment due to fatigue, alienation, and distress from this condition is on par with that of coronary artery disease [3] [8]. It is related to the release of mediators from cutaneous mast cells, mainly histamine, induced through particular IgE, the components of complement activation, as well through several nonspecific endogenous peptides, endorphins, and enkephalins [5] [7]. Trigger for CSU is often not known, but there is an association with autoimmune disease [9]. In more than 50% of CSU patients, elevated levels of IgE autoantibodies against thyroperoxidase (TPO) can be detected, which when bound and activated on the surface of mast cells, cause an autoallergic mast cell degranulation [2].

Urticarial lesions are typically pruritic, edematous pink or red wheals of variable size and shape with surrounding erythema that usually fade within one to two days, however, new lesions can be simultaneously developing elsewhere [5]. In our case, absence of renal, ocular, or abdominal symptoms, along with a normal complement level, supports this conclusion. Routine skin biopsies are not required in most cases of chronic urticaria and can be performed in refractory cases or when vasculitis or other non-urticarial immunologic skin diseases are suspected. Hypersensitivity skin or serologic testing for food or other allergens is rarely useful and not recommended on a routine basis [4]. C-reactive protein and total IgE levels are not reliable laboratory tests in predicting disease severity as they are elevated in most of the cases of chronic urticaria [10]. In our case, lack of renal, ocular, or abdominal symptoms, coupled with a regular complement level, corroborates the chronic spontaneous urticaria, excluding urticarial vasculitis. His polyarthralgia was attributed to an immune response that had precipitated the urticaria, as well as an ongoing inflammatory response in the body triggered by the release of histamines and other inflammatory mediators.

Guidelines recommend a stepwise approach to the pharmacological treatment of chronic urticaria (**Figure 2**). First-line therapy is the second-generation non-sedating oral H1-antihistamines like: bilastine, cetrizine, desloratidine, levocetrizine, rupatidine and fexofenadine [11] (Step 1). In more than 50% of the patients, symptoms persist with standard dosing of second-generation antihistamines, where updosing to fourfold the normal dose of second-generation antihistamines is recommended [2] [11] (Step 2). When the symptoms remain poorly controlled with step 2, addition of one or more of the following is recommended: H2 antihistamines, first generation H1 antihistamines at bedtime (hydroxyzine or doxepin), and/or leukotriene receptor antagonists (LTRAs like montelukast, zafirlukast and pranlukast) [5] (Step 3). If the symptoms persist for more than 4 weeks even with the step 3 therapy, addition of omalizumab or cyclosporine or other anti-inflammatory agents, immunosuppressants or biologics are recommended [4] (Step 4).

Among the available options for refractory chronic urticaria, cyclosporine has proven efficacy however, its use has been limited due to its potential side effects altering hematological parameters and decreased kidney and liver function [11]. Other therapeutic options, which have not been included in the guideline, are dapsone, hydroxychloroquine, oral steroid, methotrexate, azathioprine, mycophenolate mofetil and biologics including intravenous immunoglobulins (IVIGs), rituximab, and adalimumab [11] [12]. None of these drugs have been studied in a double bind placebo-controlled fashion in a large enough group of patients and the evidence for their convincing effect in treatment of urticaria is very low [2] [12]. Systemic corticosteroid is frequently used for patients with refractory chronic urticaria, but no controlled studies have demonstrated its efficacy and its long-term use should be avoided due to the risk of adverse effects [5]. In some patients short-term use (e.g., 1 - 3 weeks' duration) of oral steroid might be required to control disease until other therapies can achieve control [5]. Refractoriness to both Omalizumab and cyclosporine is expected to be seen in less than 5% of patients [13].

Omalizumab is a recombinant humanized IgG-anti-IgE antibody that binds human IgE causing down regulation of IgE receptor (FcεR-I) on mast cells and basophils [2] [11]. One study employed patients without autoimmunity with approximately the same response rate to omalizumab and the rationale for a response in these patients is unexplained [12]. It has been approved by the FDA at both 150 mg and 300 mg doses in the treatment of refractory CSU with or without angioedema for people twelve years of age or older [5] [11]. Omalizumab 300 mg every four weeks is considered as the most effective regimen [11]. In every fourth week, symptoms are re-evaluated and if patient's symptoms are better controlled, the interval between injections is increased up to 7 weeks after which treatment is stopped [14]. In our case, the decision to initiate the lower dose of omalizumab 150 mg, rather than the 300 mg dose, was based on a step-wise treatment approach. Our aim was to achieve adequate symptom relief

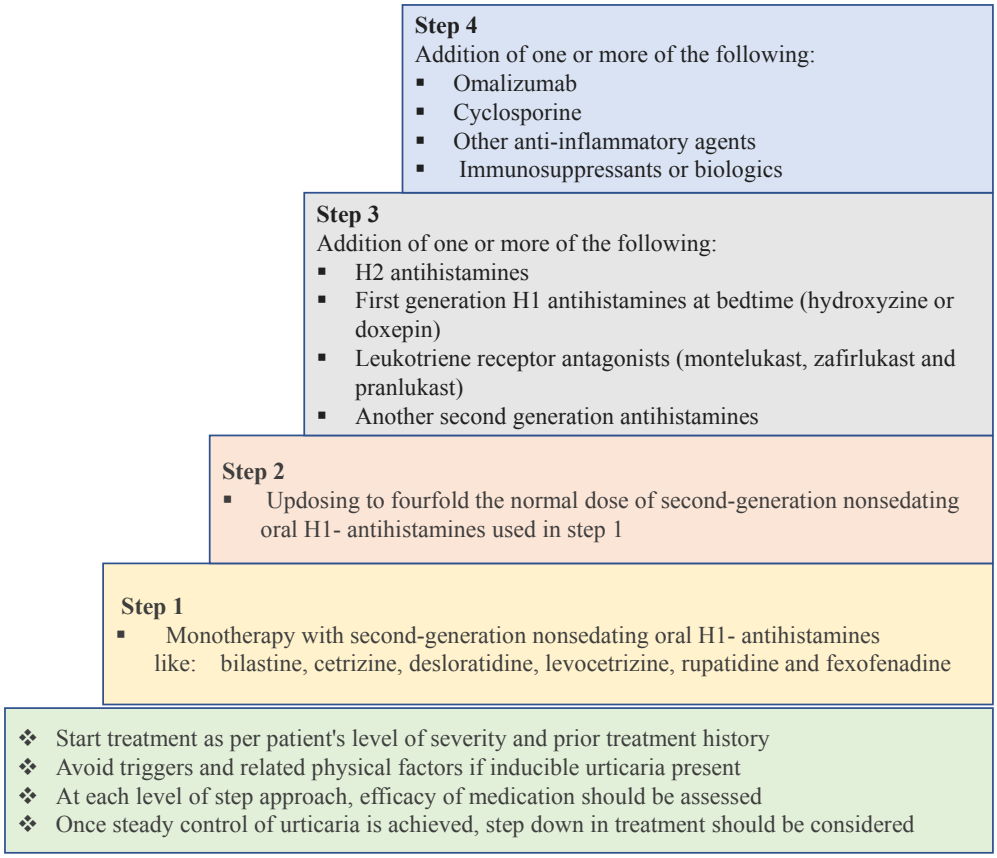

Figure 2. Stepwise approach to the pharmacological treatment of chronic spontaneous urticaria.

with the lower dose, while also minimizing the risk of potential adverse effects and taking cost considerations into account. Clinical trials investigating its long-term safety and treatment duration for CSU are currently underway [15].

A prospective observational study conducted on 93 patients with CSU revealed that 12 weeks after beginning omalizumab treatment (300 mg/4weeks), 47% had a complete response, 39% had a partial response, and 14% were non-responders [14]. Additionally, a study conducted by Kaplan *et al.* of 12 patients with chronic autoimmune urticaria who experienced persistent symptoms despite 6 weeks of antihistamine use showed that after 16 weeks of omalizumab treatments every 2 or 4 weeks, 7 achieved complete symptom resolution, 4 had decreased mean urticaria symptoms but persisted, and 1 was a non-responder, with no reported adverse effects [8].

Reports on adverse effects of long-term use of omalizumab are few [12]. Most commonly reported side effects include headaches, upper respiratory tract infections, arthralgia and irritation at the site of injection [5] [11]. Omalizumab use has no other contraindications except for severe hypersensitivity reactions [13]. According to a recent study, the use of omalizumab for treating moderate to severe urticaria is linked to significantly higher costs compared to alternative treatment options [14]. The estimated annual cost (assume 13 doses per year) of omalizumab is reported to be $7956.00 for the 150 mg dosage and $15912.00 for

the 300 mg subcutaneous dosage. In contrast, other treatment options such as cyclosporin capsules (5 mg/kg daily) cost $3769.28 and Hydroxychloroquine (400 mg daily) costs $191.26 annually [11]. Despite higher costs, omalizumab's FDA approval for treating chronic spontaneous urticaria allows patients to potentially benefit from copay programs, easing the financial burden.

The long-term impacts and best course of action for tapering or ceasing omalizumab therapy is still unknown. Dose reduction and elongating the time between dosages are possible ways of tapering [15]. Studies indicated that most patients experience severe urticarial symptoms 4 - 8 weeks after their final omalizumab injection [2]. According to Romano *et al.*, tapering to 150 mg per month and increasing the interval beyond 28 to 30 days did not provide lasting relief [10]. The OPTIMA trial, involving 314 chronic spontaneous urticaria patients who received 150 mg/300mg of omalizumab every 4 weeks for 24 weeks, revealed that 49% of the participants experienced a relapse of symptoms within 8 weeks, with the median time to relapse being 4.7 weeks after discontinuation of omalizumab [12].

Studies have shown that women, those with prolonged disease duration, high basal IgE levels and rapid treatment responders to omalizumab are likely to experience a recurrence after cessation of omalizumab treatment [11] [12]. It is uncertain, however, which patient features are linked to the probability and speed of relapse after ceasing omalizumab [15]. In this case, the patient being a female with a long-term urticaria increased her susceptibility to an early relapse, but the normal level of IgE offset the risk. Over the course of 12 months, our patient experienced a complete absence of urticaria outbreaks. This favorable outcome was achieved through an initial monthly administration of omalizumab for the first 6 months, followed by a transition to a bi-monthly schedule for the subsequent 6 months. This success instilled us with the assurance to pursue an incremental approach, whereby the interval between doses would be extended by an additional month every six months. Our plan involved extending the interval by an additional month every six months, gradually reducing the frequency with an ultimate goal of complete discontinuation of the medication.

To gain better understanding of clinical and serological markers which could potentially impact outcomes for chronic urticaria patients treated with omalizumab, larger-scale studies must be conducted [14]. Because of the potential for spontaneous remission, attempts should be made to reduce dosage of omalizumab, and generally, retreatment will quickly induce remission [9].

4. Conclusion

The efficacy of omalizumab for treating CSU is well-known; however, the length of its effects, the most suitable way of tapering and ceasing the medication, and the likelihood of relapse and remission after its discontinuation are all yet to be fully elucidated. Determination of the clinical and serological factors that influence the management of individuals who have been treated with omalizumab is

essential. By closely monitoring the clinical response to gradually reducing omalizumab over an extended period, we can establish the optimal approach for tapering and discontinuation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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