

Does Antihistamine Up-dosing Solve Chronic Spontaneous Urticaria?

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Abbreviations *IgE* Immunoglobulin E · *Ig* Immunoglobulin G · *CSU* Chronic spontaneous urticaria · *CindU* Chronic inducible urticaria · *PET* Positron emission tomography

Opinion Statement

Urticaria is primarily a disease driven by the actions of mast cell-derived histamine on the dermal vasculature and sensory nerves. Initial treatment with second generation minimally sedating H₁-antihistamines is recommended. Start with the standard dose of one tablet daily. Because of the high local levels of histamine in the skin, standard doses of H₁-antihistamines are often not able to control the symptoms. Thus, if symptoms persist after 2 weeks, then double the dosage of H₁-antihistamines, usually giving one in the morning and one in the evening. If this is still not effective after 2 weeks, double the dose to fourfold of the original dose, two tablets given approximately 12 h apart. For patients still not responsive, then other medication, such as omalizumab or cyclosporine A should be introduced. Omalizumab treatment is highlighted in this review.

Introduction

The activation of dermal mast cells and the release of their inflammatory mediators are regarded as the final common pathway in all forms of urticaria. This is supported by the findings of increased concentrations of histamine in the skin tissue fluid [1] and the clinical

responsiveness of urticaria to H₁-antihistamines.

The main option for the management of chronic urticaria of all types is pharmacological therapy aimed at symptomatic relief. The EAACI/GA2LEN/EDF/WAO urticaria guideline [2••] recommendations for drug

treatment are as follows. Modern second-generation H₁-antihistamines are the first line of treatment. If symptoms persist after 2 weeks, then the second line is to increase the dosage of second-generation H₁-antihistamines up to fourfold. If symptoms persist after 1–4

further weeks, the third line treatment is to add omalizumab, cyclosporine or montelukast on to second line. Further, a short course (max 10 days) of corticosteroids may also be used at all times if exacerbations demand this.

H₁-antihistamines

H₁-antihistamines were developed originally from anticholinergic drugs more than 70 years ago. They act as inverse agonists rather than antagonists of histamine H₁-receptors [3], i.e. histamine binds to receptor and activates it, while an H₁-antihistamine binds to a different part of the receptor to stabilize it in the inactive form and so prevent histamine activating it.

The older first-generation H₁-antihistamines, including chlorpheniramine, diphenhydramine, hydroxyzine and ketotifen, penetrate readily into the brain where they cause sedation, drowsiness, fatigue and impaired concentration and memory causing detrimental effects on learning and examination performance in children and on impairment of the ability of adults to work and drive motor vehicles [4, 5]. Also, the cumulative use of first-generation antihistamines with anticholinergic activity in the elderly is associated with an increased risk for dementia [6]. Consequently, the use of first-generation H₁-antihistamines should be discouraged. Furthermore, physicians should advise their patients not to purchase these drugs from the pharmacy for self-medication.

The newer second-generation H₁-antihistamines are safer, cause less sedation and are more efficacious. Of these, azelastine, olopatadine, cetirizine and loratadine may cause drowsiness in some individuals [7], but this is generally mild. Recent publications have suggested that, at manufacturer's recommended doses, levocetirizine is less sedating than cetirizine and desloratadine causes negligible somnolence [4]. However, it should be pointed out that 'mean results' do not reveal everything as patients are individuals and, as such, may show considerable somnolence whereas others are unaffected.

While discussing somnolence, special mention should be made of fexofenadine and bilastine. Positron emission tomography (PET) scanning has shown that the occupancy of histamine H₁-receptors in the brain of these two drugs is negligible [7, 8] and in psychomotor tests, they are not significantly different from placebo [9, 10]. This is because both drugs are substrates for P-glycoprotein, a membrane pump that limits their passage across the blood-brain barrier.

What patients require from an H₁-antihistamine is a rapid onset of action, good efficacy and a long duration of action. In general, all second-generation H₁-antihistamines have an onset of action of about 1 to 4 h. Also, they are clinically effective for at least 24 h, making once daily dosing a practicality. With regard to efficacy, very few back-to-back studies have been performed with H₁-antihistamines in CSU so comparisons are largely anecdotal. However, studies have compared levocetirizine and desloratadine

and have shown levocetirizine to be the more effective in both mild and moderate severe conic urticaria [11, 12].

Histamine released from mast cells reaches high local concentrations in the skin because of poor diffusion from the site of degranulation. This is different from histamine release at mucosal sites, for example in the nose, where the looser structure of the nasal lining facilitates histamine diffusion and consequently histamine does not build up to similarly high levels. Because of the high local levels of histamine in the skin, standard doses of H₁-antihistamines are often not able to control the symptoms. In this case, the EAACI/GA2LEN/EDF/WAO urticaria guideline [2••] recommends if symptoms persist after 2 weeks, then the second line is to increase the dosage of second-generation H₁-antihistamines up to fourfold. This is usually done in two steps. First is to increase the dose to two tablets given approximately 12 h apart and then, if the symptom control is still not achieved, increase to four tablets, again given in two divided administrations. A further point that should be made here is that H₁-antihistamines act in the same way with no other additional mechanisms of action demonstrated clinically. Therefore, mixing different antihistamines will not have additional benefits in terms of adding other potential actions. These results have to be confirmed in controlled trials. Schulz and colleagues [13] reported that the combination of H₁-antihistamines was not more effective than the high-dosage monotherapy probably due to unknown interactions and addition of side-effects in combination therapies. Also, choosing a single antihistamine, preferably the most potent one, which suits the patient [12] for up-dosing will reduce patient confusion regarding the treatment administration and help patient compliance, and, consequently, increase effectiveness [13]. In a recent study with bilastine in cold urticaria [14], increasing the daily dose fourfold from the recommended level of 20 to 80 mg decreased the critical temperature threshold to 4 °C or less in 75 % of patients with no patient reporting somnolence. This indicates that bilastine is indeed an effective drug for up-dosing. It is also important to advise your patients to take their medicines regularly rather than just when their symptoms are getting worse (on demand) [15].

Many clinicians believe that to treat urticaria effectively, a non-sedating H₁-antihistamine should be given in the morning and a sedating drug, such as hydroxyzine, should be given at night to aid sleep. However, a recent study has compared treatment with levocetirizine alone with treatment where the evening dose of levocetirizine was replaced with hydroxyzine [16]. The results showed that the regimens were similarly effective in reducing symptoms night-time sleep disturbances. However, daytime somnolence was significantly higher in patients taking an evening dose of hydroxyzine. It is clear, therefore, that it is better to aim at the effective control of urticaria symptoms with a non-sedating antihistamine than to offer a sedating antihistamine at night.

In conclusion, the current standard therapy with regularly dosed H₁-antihistamines leads to an absence of symptoms in <50 % of patients with chronic spontaneous urticaria. Increasing the dose up to fourfold improves

treatment responses but still every third to fourth patient will remain symptomatic [17]. In these patients, a trial of montelukast is a possible option, especially in non-specialist settings. However, if no benefit is noticed in 4–6 weeks, this treatment is unlikely to show further benefits. In this situation or if patients experience severe symptoms despite stepping up the H₁-antihistamine dose, it is recommended to refer the patient to an allergy specialist centre where one of the other third-line therapies can be offered, i.e. omalizumab or cyclosporine. This review will consider only omalizumab.

Omalizumab in Chronic Urticaria

Omalizumab is a humanized, monoclonal, anti-IgE antibody comprising a human IgG framework onto which has been grafted the complementarity-determining regions from a murine anti-IgE antibody [18••, 19]. Omalizumab binds to free IgE in the blood and interstitial space, forming biologically inactive IgE complexes that are unable to bind to FcεRI on the surface of mast cells and basophils [18••, 20••]. Omalizumab, which was originally introduced for treating IgE-mediated allergic diseases and approved for treating patients with severe persistent allergic asthma in many countries, reduces the amount of free IgE that may bind to mast cells and basophils and enable them to be triggered for degranulation [20••].

Up to the present time, two phase II and four phase III multicentre, randomized, placebo-controlled clinical trials [18••] have convincingly established that omalizumab is efficacious and safe for treating CSU that cannot be adequately treated with H₁-antihistamines.

To gain a deeper perspective of omalizumab in clinical usage, we recently performed a retrospective clinical analysis of 51 antihistamine-resistant patients in Germany in which we assessed responder rates, optimal dosage, response to up-/down-dosing, time to relief of symptoms, rates of return and time of relapse after omalizumab administration and safety [21]. Of the 51 chronic urticaria patients assessed, 20 had CSU alone, 21 had different forms of chronic inducible urticaria (CindU) and 10 had both. The results showed that omalizumab treatment led to total remission in 83 % of CSU and 70 % of CindU patients. When starting with 150 mg omalizumab 4 weekly, only 2/15 CSU and 7/17 CindU patients required up-dosing to achieve complete remission. In CSU, 57 % of complete responses occurred within week one, all on the first day. Interestingly, efficacy was not correlated to baseline IgE levels. No unwanted effects were noted. Consequently, we concluded from our clinical experience from more than 1250 injections in 51 patients over 4 years that omalizumab is a rapidly acting, highly effective and safe drug in CSU and CindU patients. In a separate study of 18 patients [22], the duration of effectiveness following a single injection of omalizumab peaked at 4–5 weeks. This indicates that omalizumab does not ‘cure’ chronic urticaria but only suppresses the generation of symptoms whilst present in the body at effective concentrations.

But how does anti-IgE suppress the symptoms of a condition of which an allergic basis is somewhat speculative? Some 30 years ago, Grattan and

colleagues [23] reported that when autologous serum was injected into the skin it produced a wheal and flare response. This is the so-called autologous serum skin test (ASST) [24]. In adults, the prevalence of positive ASST reactivity in patients with CSU is approximately 45 % [24]. Analysis of the serum indicated that the ASST was due to the presence of IgG autoantibodies against FcεRI, IgE or both, which can cross-link IgE-occupied or unoccupied FcεRI to activate mast cells and basophils [25]. Interestingly, the IgG subclasses that appear to be pathogenic are IgG1 and IgG3 [26, 27], both of which are capable of activating complement C5a, a known stimulator of skin mast cells, but not other mast cells, in human subjects [28]. In the presence of omalizumab, there is a slow loss of mast cell-bound IgE followed by a slower loss of FcεRI on the surface of mast cells and basophils [29]. Consequently, these cells will no longer be able to be activated by IgG autoantibodies and urticarial symptoms will no longer be seen. This may be an explanation for the slower response (days to weeks), as is seen in many cases of omalizumab treatment [18••].

The mechanism of the faster response to omalizumab is, as yet, still unclear. However, two possibilities have been mooted. The first is that urticaria is caused by local autoallergens in the skin. It is known that many urticaria patients have high IgE levels to autoantigens, such as thyroperoxidase and double-stranded DNA [20••, 30]. By forming inactive hexa-complexes with IgE, omalizumab can sequester free autoallergens and, if they are involved in causing urticaria, cause a rapid reduction of symptoms [18••].

Other studies have extended into humans the suggestion that mouse monoclonal IgE molecules are heterogeneous with respect to their ability to induce survival and activation events in mast cells [31]. At one end of the spectrum, highly cytokinergic (HC) IgEs induce enhanced survival, degranulation, adhesion, migration and expression of cytokines, such as IL-6 and TNF-α. At the other end of the spectrum, poorly cytokinergic IgEs mediate these effector functions inefficiently [32]. Interestingly, most murine monoclonal HC IgEs exhibit reactivity to autoantigens, such as double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), β-galactosidase, thyroglobulin and histamine-releasing factor. Autoantibodies to such autoantigens are often also found in patients with autoimmune diseases. By contrast, poorly cytokinergic IgEs do not react with these antigens. This IgE heterogeneity is not restricted to murine antibodies: Kashiwakura and colleagues [33] recently reported that a human monoclonal HC IgE also shows polyreactivity to dsDNA, ssDNA and histamine-releasing factor. It is tempting to speculate that a reduction of high cytokinergic IgE by omalizumab may also induce rapid relief from urticaria.

Conclusion

In conclusion, it is clear that although many CSU patients are helped greatly by H₁-antihistamines, particularly at higher doses, not all are responsive. The reason for this is not yet clear. However, the introduction of omalizumab into the clinicians' armoury means that they may help the majority of H₁-antihistamine non-responsive patients.

Compliance with Ethics Guidelines

Conflict of Interest

Martin Church has been a speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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