Clinical and Experimental Dermatology and Therapies
Vashurin I, et al. Clin Exp Dermatol Ther 7: 177.
www.doi.org/10.29011/2575-8268.100177
www.gavinpublishers.com

Research Article

Body Mass Index as Omalizumab's Efficacy Predictor in Chronic Spontaneous Urticaria

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Citation: Vashurin I, Barzilai A, Pavlotsky F (2022) Body Mass Index as Omalizumab's Efficacy Predictor in Chronic Spontaneous Urticaria. Clin Exp Dermatol Ther 7: 177. DOI: 10.29011/2575-8268.100177

Received Date: 26 March 2022; **Accepted Date:** 12 April 2022; **Published Date:** 14 April 2022

Abstract

Introduction: Approximately, 30% of chronic spontaneous urticaria patients are non-responders to omalizumab treatment. **Objectives:** The study focuses on identifying possible predictors of omalizumab efficacy. **Methods:** This retrospective study involves patients with chronic spontaneous urticaria who were treated with omalizumab in a day-care setting. Data was collected and analyzed using the MD Clone ADAMS platform. This included demographic (age, sex), clinical (body mass index (BMI), IgE, comorbidities), laboratory, and therapy-response parameters such as the rate of complete response, omalizumab dosage, and additional treatments needed, and side effects. **Results:** Overall, 62.5% of patients had a complete response to the standard omalizumab regimen (up to 300 mg once every 4 weeks). Among non-complete responders, 75% had abnormal BMI (13 overweight and 14 obese patients) versus 40% among complete responders ($p<0.01$) with a linear correlation. Higher BMI values indicated lower efficacy ($p<0.05$). Age, sex, IgE values, disease stage, other metabolic syndrome parameters (besides BMI), atopic diathesis, and autoimmune diseases were not found to influence treatment efficacy. **Conclusions:** Higher BMI is a significant negative predictive factor for omalizumab efficacy in chronic spontaneous urticaria.

Keywords: BMI; Chronic spontaneous urticaria; Omalizumab; Obesity; Overweight.

Introduction

Available treatment options for chronic spontaneous urticaria (CSU) are second-generation antihistamines (SGA) (first line), up to four times the standard dose of SGA (second line), systemic steroids or disease-modifying antirheumatic drugs (DMARDs) (third line in Israel), and omalizumab (3rd line in many countries, 4th line in Israel) [1,2].

Omalizumab with approximately 70% success in clinical trials is an effective treatment for chronic CSU [2].

Until present times, there is a paucity of data regarding the factors that might lead to treatment failure in the remaining patients in general and, in particular, in the real-world setting. Therefore, the present study aimed to identify possible predictive factors for omalizumab efficacy in CSU.

Methods

This retrospective single-center study involves CSU patients, treated with omalizumab in a day-care setting between 2016 and 2021 who failed four times the SGA standard dose and a minimum of one immunosuppressant (mainly methotrexate or cyclosporine), and/or montelukast (Israeli's health maintenance organization requirements).

Omalizumab was administered without interrupting the previous treatment, and we gradually stopped the previous treatment after achieving a complete response (CR) (total disappearance of urticarial lesions and pruritus). Subsequently, omalizumab inter-treatment intervals were slowly increased until the treatment was completely withdrawn. Patient data were collected from the computerized patient files using MD Clone, data extraction and synthesis platform that provides patient-level data around an index event (http://www.mdclone.com). Data on patients' age, sex, pre-treatment immunoglobulin E (IgE) values, body mass index

(BMI), other metabolic syndrome components (diabetes mellitus, dyslipidemia, and hypertension), atopic diathesis, autoimmune disorders, CSU duration, omalizumab dosage/frequency, previous continued treatments, and side effects were collected [3]. BMI values over 24.9 and 29.9 were considered overweight and obese, respectively [4]. IgE values below 145 IU/mL were considered normal [5].

Prism (version 8.4.3) from GraphPad Software was used to perform statistical data analysis. The chi-square test was used to assess treatment efficacy following parameters such as sex, BMI, IgE, and presence of comorbidities. The ANOVA test was also used to assess the difference between treatment periods and between dosages. Simple linear and logistic regression tests were used to assess the relationship between BMI values and sex, age, IgE values, and the rate of CR to treatment. A p-value of ≤ 0.05, was considered statistically significant. The study was approved by the local institutional ethics committee (7524-20-SMC). Written informed consent was not needed.

Results

Out of 96 patients included in this study, 71.8% were women, with an average age of 48.7 ± 17.14 years. Males had a similar mean age of 48.2 ± 16.2 years. Only 46.8% of the patients had normal BMI values, while 25% and 28.1% were overweight and obese. Twenty-two patients (23%) had one or more components of metabolic syndrome, 13 (13.5%) had one or more components of atopic diathesis, 9 (9.3%) had an accompanying autoimmune disease, 4 (4.1%) had non-active viral hepatitis, and one patient had epilepsy. Among 76 patients who had pre-treatment IgE values, 45 (59.2%) had normal values. Most patients had undergone at least one concomitant anti-CSU treatment. Thus, 62 patients (64.5%) were treated with SGA, 14 (15%) with DMARDs, and 5 (5%) were co-treated with systemic steroids.

Sixty patients (62.5%) achieved CR within a median of 3.7±5.1 months with standard dosage and administration intervals. Of 18 patients (18.7%), CR was reached within a median of 4.1 ± 1.9 months only after dose escalation over 300 mg/treatment and/or decreasing the inter-treatment interval to 3 weeks. Thus, 78 patients (81.2%) achieved CR.

Among patients with normal BMI values, 37 had CR (82.2%) in comparison to 11/24 (45.8%) and 13/27 (48.1%) of overweight and obese patients, respectively, who had CR ($p<0.01$) (Table 1). Eight patients (8.3%) had a partial response (PR) with standard dosing, and another 5 (5.2%) achieved it after dose escalation and/or a decrease in inter-treatment interval. Overall, 7 patients needed 450 mg/treatment and one severely obese patient required 600 mg/treatment. Thirteen patients were treated every 3 weeks, out of which 2 patients needed dose escalation and a decrease in inter-treatment interval. Five patients (5.2%) showed no response at all.

In general, 23 patients (24%) required dosage escalation or a decrease in inter-treatment interval, while 16 (70%) had abnormal BMI values; among them, 13 patients (81%) reached CR ($p=0.62$).

Among patients with normal IgE values, 31/45 (68.8%) compared to 15/31 patients (48.3%) with abnormal IgE values had CR, but the difference was not statistically significant ($p=0.09$) (Table 1).

Patients' characteristics		CR (n = 60)	PR/no response (n = 36)	P-value
Gender % (n)	Males (n = 27)	63 (17)	37 (10)	0.9999
	Females (n = 69)	62.3 (43)	37.6 (26)	
Mean age +/- SD (years)		49.6 +/- 17.2	46.8 +/- 16.4	0.4389
BMI % (n)	Normal (n = 45)	82 (37)	18 (8)	0.0017*
	Overweight (n = 24)	46 (11)	54 (13)	
	Obese (n = 27)	48 (13)	52 (14)	
Comorbidities % (n)	Other metabolic syndrome components (n = 22)	59 (13)	40 (9)	0.7728
	Atopic diathesis (n = 13)	69.2 (9)	30.7 (4)	
	Autoimmune diseases (n = 9)	55.5 (5)	44.4 (4)	
IgE† % (n)	Normal values (n = 45)	68.8 (31)	31 (14)	0.0959
	High values (n = 31)	48.3 (15)	51.6 (16)	

† IgE reference range is 1.5–144 IU/mL; *Statistically significant ($p < 0.05$).

Table 1: Response rate adjusted to age, gender, comorbidities and IgE.

Logistic regression analysis revealed no significant association between age, sex, IgE level, presence of comorbidities, and a chance of achieving CR. However, there was a highly positive and significant association with normal BMI values, and the inverse association between CR rate and BMI was shown to be linear ($p<0.05$) (Figure 1). Four patients (4.1%) had allergic reactions to omalizumab treatment. No other serious side effects were reported.

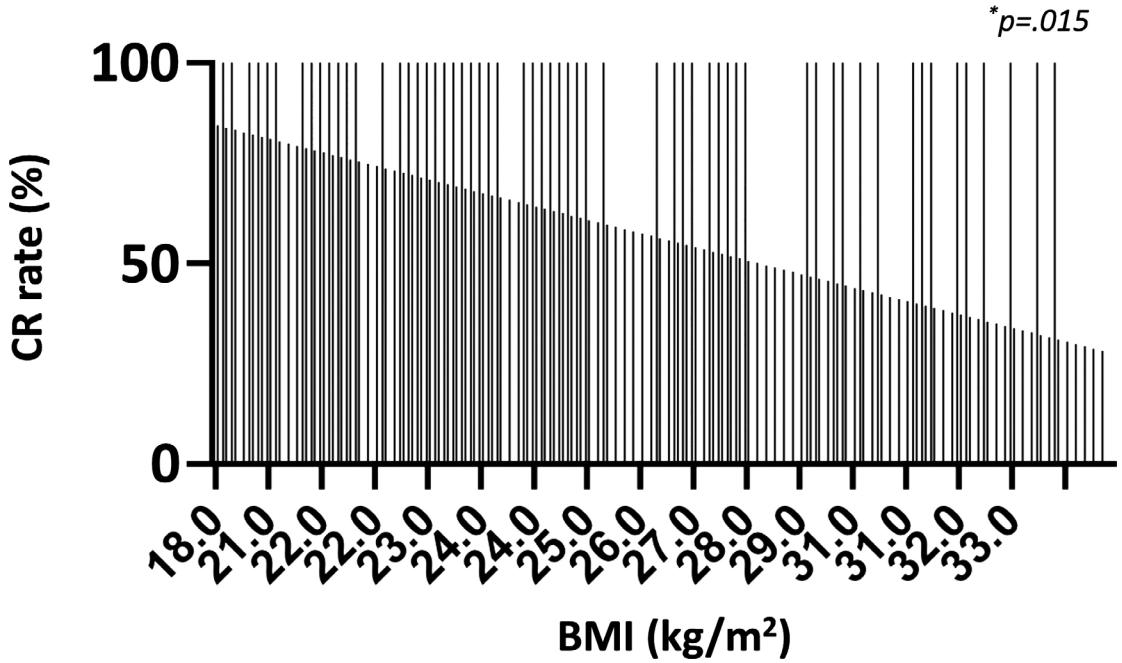

Figure 1: Complete response rate in correlation with BMI.

Discussion

Urticaria is a common disease characterized by a sensation of pruritus or burning with the appearance of wheals (hives), angioedema, or both [2,6].

Unrecognized contributing conditions along with symptoms lasting for at least 6 weeks lead to the diagnosis of chronic urticaria, which is divided into CSU and chronic inducible urticaria (CindU) [2,6-8].

The pathogenesis of CSU is not well established; however, mast cells and basophils are considered to be the main effector cells that release numerous mediators upon activation, including histamine, which is considered the main mediator in the pathogenesis of urticaria [2,7,9]. In CSU, activation of mast cells and basophils appears to occur via cross-linking of IgE antibodies and immunoglobulin G (IgG) autoantibodies against bound IgE and IgG autoantibodies against high-affinity IgE receptor (FcεRI) [9,10].

Omalizumab is a 3rd- 4th line (local regulation dependent) therapy for CSU. It is a recombinant IgG1k monoclonal antibody that targets IgE, hence reducing its number and inhibiting the activation of FcεRI on mast and basophil cells [2,8,11,12]. It is also thought to prevent IgG autoantibody-mediated cell activation [12].

According to a phase II study, MYSTIQUE, and phase III studies, ASTERIA I, ASTERIA II, and GLACIAL, a 300 mg monthly dosage of omalizumab helped achieve a response rate of approximately 80%, 51.9%, 53%, and 52.4% respectively [11-15]. In our real-life study, a higher CR rate of 62.5% was achieved with the same dosage. Furthermore, CR was achieved in a total of 78/96 patients (81.25%) after dose escalation over 300 mg/treatment and/or a decrease in the inter-treatment interval to 3 weeks in patients with an insufficient response.

Despite the efficacy of omalizumab, a minimum of one-third of the patients in our and previous studies showed insufficient response with standard dosing [1,2,11-15]. Few studies have

examined the predictive factors of omalizumab efficacy in CSU. Omalizumab was less effective in asthmatic patients with higher IgE levels and body weight or concomitant use of angiotensin-converting enzyme (ACE) inhibitors [16-18]. The latter can be attributed to either bradykinin inhibition by ACE inhibitors or as a marker for metabolic syndrome. In the study by Magen et al. [19], few factors associated with omalizumab resistance were analyzed. In general, 59% of CSU patients had CR, while the non-responsive patients were characterized by a higher rate of obesity, arterial hypertension, and higher C-reactive protein (CRP), C3, and white blood cell levels. However, only CRP levels (and not obesity) were found to be significant in their multivariate analysis. In our retrospective study, CR to omalizumab was achieved in 62.5% of patients, while 75% of non-CR individuals had significantly higher and abnormal BMI values (overweight or obese). The inverse and significant association between CR and BMI was linear. Similarly, 70% of patients requiring dose escalation and/or a decrease in the inter-treatment interval to achieve CR had abnormal BMI values. There was no significant association between patients' age, sex, IgE level, or the presence of examined comorbidities (besides BMI). It should be noted that information regarding IgE values in our study was available only in 79% of patients, which can influence the final result.

The efficacy of other biological agents was reported to be influenced by BMI. Meta-analyses have demonstrated that tumor necrosis factor (TNF) blockers are less effective in obese patients. Even though the exact reason is still unclear, it seems that the lipophilic properties of different biological agents may explain this phenomenon. Another explanation is that obesity promotes Th17 differentiation and IL-17 production, which leads to systemic inflammation and poorer therapeutic response to TNF blockers [20,21]. The exact mechanism explaining omalizumab's poorer response in obese patients is unclear.

One possible hypothesis is that the non-lipophilic properties of omalizumab make it less distributed in obese patients. Omalizumab has a bioavailability of 62%, while drug metabolism occurs in the hepatic reticuloendothelial system [16], and the specific enzymes have not yet been defined. In overweight and mostly obese patients, fatty liver may alter the cytochrome P450 enzyme family activity, which metabolizes approximately 75% of all drugs [22]. Moreover, obese patients have increased hepatic blood flow, with alterations in other enzymes involved in drug metabolism. Enzyme levels of the cytochrome P2E1 family, phase II reactions, glucuronidation, and sulfation are increased with obesity [23].

One possible solution is the addition of another immune-modulating agent or dose modification, as shown in our study [24]. Limitations of the present study include its retrospective, single-center nature and local HMO requirements somewhat different from the recommended in most of the other countries.

Conclusion

We conclude that the CR rate for omalizumab in CSU is BMI dependent and could be improved by dose adjustment in less responsive cases. Further prospective double-blinded and BMI dose-adjusted studies are needed.

Acknowledgments

The research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

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