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ORIGINAL ARTICLE

The effect of COVID-19 on patients with chronic spontaneous urticaria treated with omalizumab and antihistamines: A cross-sectional, comparative study

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Abstract

Introduction: Chronic spontaneous urticaria (CSU) is defined as recurrent attacks of urticaria present for more than six weeks. The monoclonal anti-immunoglobulin E antibody, omalizumab, was approved for the treatment of CSU in patients who remain refractory to H1-antihistamines. Biologic agents are shown not to increase the risk of COVID-19 infection in different studies.

Objective: In the present study, we aimed to determine the prevalance of COVID-19 infection in relation to the age, gender, presence of other comorbidities, and treatment given for CSU.

Methods: We conducted a descriptive cross-sectional study of 233 patients diagnosed with CSU in a tertiary referral hospital. Demographical data, treatment given for CSU, the presence of COVID-19-related symptoms, history of close contact to a person with COVID-19 and COVID-19 real-time polymerase chain reaction (RT-PCR) results were determined via a telephone survey and checked from medical data records.

Results: One hundred sixty patients were female; whereas 73 were male. The mean age was 44.76. Out of 233 patients with chronic urticaria, 125 had symptoms related to COVID-19 infection. RT-PCR testing for COVID-19 was performed in 156 patients. Of 156 patients with COVID-19 RT-PCR test, RT-PCR result was positive in 15 cases.

Conclusions: No statistically significant relationship was found between COVID-19 RT-PCR positivity and the type of treatment administered for chronic urticaria when the patients are divided into omalizumab ± oral antihistamines and only oral antihistamines treatment groups ($p = 0.150$). Omalizumab seems to be safe in the era of COVID-19.

KEYWORDS
chronic urticaria, COVID-19, omalizumab

The study was conducted at Department of Dermatology and Venereology, Hacettepe University, Faculty of Medicine, Ankara, Turkey.

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is a chronic, most commonly idiopathic skin disorder characterized by repetitive episodes of wheal, angioedema, or both present for >6 weeks.[1] Since CSU is mainly characterized by intensive pruritus and may be associated with systemic symptoms such as fever, malaise, joint pain, wheezing and sleep problems, the disease has a great impact on the life quality and daily functioning of the patients.[2] The vasodilatation, inflammatory cell infiltration, increased vascular permeability, erythema, and edema triggered by mast cell-related mediators including histamine, various cytokines, and platelet-activating factor play the substantial role in the etiopathogenesis of CSU.[1] Autoimmune diseases, chronic infectious diseases, functional autoantibodies, and immune dysfunction have all been implicated in the development of chronic urticaria.[1,3] However, most cases of CSU are shown to remain idiopathic even after long periods of follow-up.[3]

Second-generation H1-antihistamines are the first-line treatment of the CSU; up-dosing of second-generation H1-antihistamines up to fourfold are recommended for the patients who remain unresponsive to standard, onefold dose of H1-antihistamines.[1] When there is no improvement with fourfold dose increase, omalizumab is recommended as add-on therapy.[1] Omalizumab is a humanized monoclonal anti-immunoglobulin (Ig) E antibody which selectively targets free human Ig E.[4] Even though approved primarily for the treatment-resistant allergic asthma, it is shown to be efficacious in CSU cases[5] which are unresponsive to the first-line H1-antihistamines and also licensed for CSU in 2014.[6] Omalizumab is shown to exert its effect on CSU by lowering IgE levels, downregulate IgE receptors, decrease the activity of mast cells and IgG autoantibodies which are directed against high-affinity IgE receptors (FcεRI).[7]

The safety of biologic agents used for diverse dermatological indications, such as psoriasis, CSU, hidradenitis suppurativa, and atopic dermatitis, is one of the most frequently investigated issues during the COVID-19 pandemic. It is suggested to continue the ongoing therapy with biologic drugs unless COVID-19-related symptoms are reported by the patients.[8] If patients present with symptoms suggestive of COVID-19 such as high fever, dry cough, myalgia, malaise, olfactory, and/or gustatory dysfunction; it is adviced to suspend the biologic drugs immediately.[8,9] Maintaining physical distancing, using protective equipment, practicing good hygiene, following the rules for isolation and quarantine are strongly recommended for patients using immunosuppressive or immunomodulatory drugs.[8] Omalizumab is shown to reduce the duration of human rhinovirus infection and viral spread thereby decreasing the frequency of systemic complications.[10] Furthermore, omalizumab is shown to enhance the antiviral activity of plasmacytoid dendritic cells by inducing the production of interferon-alpha.[11]

In the present study, we aimed to determine the prevalence of COVID-19-related symptoms and COVID-19 real-time polymerase chain reaction (RT-PCR) positivity among CSU patients in relation to the age, gender, disease (CSU) duration, treatment duration, kind of treatment given for CSU. Thus, we tried to determine if omalizumab confers risk for COVID-19 infection compared to the traditional oral antihistamine therapy.

2 | METHODS

The present study was a comparative, cross-sectional study which involved 233 patients with CSU followed up in our dermatology outpatient clinic. Ethics committee approval was obtained for the study (the date, project number, decision number: 4.5.2021, GO 21/604, 2021/10-23). All participants were diagnosed with CSU and receiving treatment at our center's chronic dermatologic diseases outpatient clinic between January 2015 and June 2021. The data belonging to the CSU patients was extracted from electronic medical data records. A questionnaire consisting of 14 questions was constructed (Supplementary File 1). Demograpical data, medical history, recent medications, disease duration, treatment duration, and treatment given for CSU, the presence of COVID-19-related symptoms, history of close contact to a person with a confirmed diagnosis of COVID-19 and COVID-19 real-time polymerase chain reaction (RT-PCR) results were determined via a telephone survey and also checked from the electronic medical data records. Oral informed consent was taken from all participants before the start of the questionnaire. Only patients who were receiving active-continuous treatment for CSU during the COVID-19 pandemic, were included in the study.

For statistically analysis, IBM SPSS for Windows version 20.0 was used. Categorical variables were shown as percentages and frequencies. Numerical variables were given as mean ± standard deviation (minimum-maximum). Shapiro–Wilk test was used to determine the distribution of numerical variables. Fisher's exact test or chi-square test was used to compare the differences between patients receiving different types of treatment for CSU (categorized into 3 groups: only omalizumab, only oral antihistamines, and both oral antihistamines and omalizumab). Binary logistic regression analyses (in which age, gender, the presence of any other systemic disease and given treatment) were performed taking COVID-19 RT-PCR result (positive or negative) as the dependent variable. *p*-values below 0.05 were considered statistically significant.

3 | RESULTS

A total of 233 patients diagnosed with chronic urticaria, were included in the study. The mean age was 44.76 ± 14.16 years (range: 18–80); the mean duration of the treatment for chronic urticaria was 29.18 ± 27.85 months (range: 1–180), and the average duration of the disease was 55.06 ± 53.16 months (range: 1–300). One hundred sixty (68.7%) patients were female; whereas 73 (31.3%) were male. During the era of COVID-19, 29 (12.4%) cases were solely on omalizumab treatment; 95 (40.8%) were only receiving regular oral antihistamines whereas 109 (46.8%) were on both omalizumab and

oral antihistamine treatment. Of 138 patients treated with omalizumab, omalizumab was being administered 300 mg subcutaneously every two weeks in 2 patients; 450 mg subcutaneously every four weeks in 3 patients and 300 mg subcutaneously every six weeks in 3 patients. The dose regimen was 300 mg every four weeks for the other patients. The distribution of oral antihistamine types used by the patients is shown in Table 1.

Three (1.3%) patients had history of ovarian cancer, acute lymphoblastic leukemia, and duodenal cancer, respectively, which were all cured currently. Twenty-three (9.9%) had respiratory disease most commonly being asthma, allergic rhinitis whereas 42 (18%) had cardiovascular disease most frequently being coronary artery disease, heart failure, and hypertension. Endocrine disorders, such as diabetes mellitus, autoimmune thyroiditis, and hyperlipidemia, were present in 40 (17.2%) patients whereas 8 (3.4%) out of 233 patients had rheumatologic disease including rheumatoid arthritis (RA) (2 patients), systemic lupus erythematosus (SLE) (1 patient), Sjögren's disease (1 patient), ankylosing spondylitis (AS) (1 patient), Familial Mediterranean fever (FMF) (1 patient), and osteoarthritis (OA) (2 patients).

Out of 233 patients with chronic urticaria, 125 (53.6%) had symptoms related to COVID-19 infection such as fever, malaise, sore throat, dry cough, diarrhea, headache, and myalgia. One hundred thirty (55.8%) patients had a history of close contact to a person with confirmed COVID-19 diagnosis. Real-time polymerase chain reaction (RT-PCR) testing for COVID-19 was performed in 156 (67%) patients.

Of 156 patients with COVID-19 RT-PCR test, RT-PCR result was positive in 15 (9.6%) cases, whereas the test result was negative in 141 (90.4%) patients. Of 156 cases who had COVID-19 RT-PCR test, 107 (68.6%) had COVID-19 symptoms whereas 108 (69.3%) has a history of close contact to someone with a confirmed diagnosis of COVID-19. RT-PCR test result was positive in 14% of the patients with COVID-19 symptoms, whereas the test result was positive 13.9% of the patients with a history of close contact to a person with COVID-19 diagnosis. Only two patients were hospitalized for COVID-19. The other 13 patients with a positive RT-PCR test, had mild disease and outpatient care was recommended. Omalizumab was suspended in all cases with a positive test result.

TABLE 1 Distribution of patients in relation to the type of antihistamines used for chronic urticaria

Antihistamine name	Number of patients (n)	Percentage of patients (%)
Desloratadine	55	26.96
Cetirizine	53	25.98
Bilastine	42	20.59
Rupatadine	22	10.78
Levocetirizine	16	7.84
Ebastine	7	3.43
Fexofenadine	6	2.94
Loratadine	2	0.98
Clemastine	1	0.49

The most common antihistamines were desloratadine ($n = 55$, 26.96%), followed by cetirizine ($n = 53$, 25.98%) and bilastine ($n = 42$, 20.59%).

There was no statistically significant relationship between gender vs COVID-19 RT-PCR positivity ($p = 0.109$) and between age and COVID-19 RT-PCR positivity ($p = 0.133$) (Table 2). No statistically significant relationship was found COVID-19 RT-PCR positivity and the type of treatment administered for chronic urticaria when the patients are divided into omalizumab, omalizumab along with oral antihistamines and only oral antihistamines groups ($p = 0.150$) (Table 3). There was no statistically significant relationship between COVID-19 RT-PCR results and the presence of previous malignancy, respiratory diseases, cardiovascular diseases, endocrine disorders, and rheumatologic disorders ($p > 0.05$). We found a statistically significant relationship between COVID-19 RT-PCR results and the mean duration of chronic urticaria treatment ($p = 0.020$) (Table 4). The patients with negative RT-PCR results had a higher mean duration of treatment compared to the ones with positive RT-PCR results. We found no statistically significant relationship between the presence of COVID-19 symptoms and the mean age ($p = 0.108$), the gender ($p = 0.422$) and the type of treatment given for chronic urticaria ($p = 0.802$). Additionally, there was no statistically significant relationship between the presence of COVID-19 symptoms and the presence of previous malignancy, respiratory diseases, cardiovascular diseases, and endocrine disorders ($p > 0.05$). However, statistically significant relationship was found between the presence of COVID-19 symptoms and having a rheumatologic disorder ($p = 0.026$). The patients with a history of rheumatologic disorder were shown to present with COVID-19 symptoms at a significantly lower rate compared to the ones with no rheumatologic disorders. Of note, two patients with RA were having oral methylprednisolone and leflunomide; one patient with SLE was receiving hydroxychloroquine, one case with Sjögren's syndrome and one case with FMF were using colchicine, two patients with a diagnosis of OA, were receiving non-steroidal anti-inflammatory drugs whereas one patient with AS was undergoing adalimumab treatment concurrently. No other patients in the whole group were receiving any other immunomodulatory or immunosuppressive treatment simultaneously. As expected, there seems to be a statistically significant relationship between the presence of COVID-19 symptoms and COVID-19 RT-PCR positivity ($p = 0.003$) whereas a statistically significant relationship was also found between the history of close contact to someone with a confirmed COVID-19 and COVID-19 RT-PCR positivity ($p = 0.006$) (Table 5).

Binary logistic regression analyses (in which age, gender, the presence of any other systemic diseases and given treatment) were also performed taking COVID-19 RT-PCR result (positive or negative) as the dependent. Being at an age older than 45 years was shown to be associated with an increased risk of getting a positive COVID-19 RT-PCR 3.619 fold (OR, 3.619; 95% confidence interval, 1.076–12.175); $p = 0.038$). Gender, the presence of any other systemic disease and the given treatment (grouped as only omalizumab, only oral antihistamines, and both omalizumab and oral antihistamines) were not

TABLE 2 COVID-19 RT-PCR results in relation to the mean age and gender

COVID-19 RT-PCR Results	Number of patients (n)	Age (years)*				Gender**	
		Mean	Standard deviation	Minimum	Maximum	Female n (%)	Male n (%)
Positive	141	43.71	13.466	18	74	7 (6.9)	8 (14.8)
Negative	15	48.93	13.535	22	75	95 (93.1)	46 (85.2)
Total	156	44.21	13.517	18	75	102 (100)	54 (100)

There was no statistically significant relationship between the mean age vs COVID-19 RT-PCR results ($p = 0.133$)*and the gender vs COVID-19 RT-PCR results ($p = 0.109$)**.

TABLE 3 COVID-19 RT-PCR results in relation to the different groups of treatment used for chronic urticaria

COVID-19 RT-PCR Results	Treatment groups		
	Only omalizumab *n* (%)	Only oral antihistamines *n* (%)	Omalizumab and oral antihistamines n (%)
Positive	0	9 (14.3)	6 (8.1)
Negative	19 (100)	54 (85.7)	68 (91.9)
Total	19 (100)	63 (100)	74 (100)

No statistically significant relationship was found COVID-19 RT-PCR positivity and the type of treatment administered for chronic urticaria when the patients are divided into omalizumab, omalizumab along with oral antihistamines and only oral antihistamines treatment groups ($p = 0.150$).

TABLE 4 The comparison of COVID-19 RT-PCR status in relation to the treatment duration and the disease duration for chronic urticaria

		COVID-19 RT-PCR Results		
		Negative	Positive	Total
	Number of Patients	141	15	156
The treatment duration (months)	Mean	29.99	18.13	28.85
	Standard deviation	23.642	21.507	23.641
	Minimum	1	1	1
	Maximum	120	60	120
The disease duration (months)	Mean	51.78	42.20	50.86
	Standard deviation	51.373	42.937	50.58
	Minimum	1	2	1
	Maximum	300	120	300

The patients with negative RT-PCR results have a higher mean duration of treatment compared to the ones with positive RT-PCR results ($p = 0.020$). No statistically significant relationship was found between COVID-19 RT-PCR results and the mean duration of chronic urticaria disease ($p = 0.254$).

shown to be associated with an increased risk of getting a positive COVID-19 RT-PCR test result.

4 | DISCUSSION

COVID-19 is a multisystemic, inflammatory disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[12] In December 2019, cases of pneumonia without an identified cause have emerged in Wuhan city of China.[13] Later, the etiologic viral agent was found to be SARS-CoV-2.[13] Clinical findings of COVID-19 are the consequences of immune system dysregulation, complement activation, and coagulation system induction.[14] The clinical findings may range from mild flu-like illness to severe dyspnea, thromboemboli, respiratory failure, and death.[12] Therefore, identifying the most vulnerable patients, the associated comorbidities/medications and risk factors for mortality have become one of the main objectives of the clinical investigations in the era of COVID-19. The independent risk factors for mortality were found to be older age, male sex, intensive care unit (ICU) admission, the presence of chronic obstructive pulmonary disease, hypercholesterolemia, and type 2 diabetes mellitus.[15] Patients with various chronic illnesses which require them to use immunosuppressive drugs such as methotrexate, azathioprine, cyclosporine, biologic

TABLE 5 Statistically significant relationships were found between COVID-19 RT-PCR results and the presence of COVID-19-related symptoms ($p = 0.003$) and history of close contact to someone with a confirmed diagnosis of COVID-19 ($p = 0.006$)

	COVID-19 related symptoms		Close contact to someone with a diagnosis of COVID-19		
COVID-19 RT-PCR Results	Not present *n* (%)	Present *n* (%)	Not present *n* (%)	Present *n* (%)	Total *n* (%)
Positive	0 (0)	15 (14)	0 (0)	15 (13.9)	15 (9.6)
Negative	49 (100)	92 (86)	48 (100)	93 (86.1)	141 (90.4)
Total	49 (100)	107 (100)	48 (100)	108 (100)	156 (100)
	p value = 0.003		*p* value = 0.006		

agents/monoclonal antibodies, and small molecules (apremilast and Janus kinase inhibitors) are highly recommended to maintain physical distancing, practise good hygiene and use protective devices.[8]

Psoriasis, hidradenitis supurativa, chronic urticaria, atopic dermatitis, autoimmune bullous skin diseases, and alopecia totalis are some of the chronic skin diseases which mostly necessitate long-term administration of systemic immunosuppressive or immunomodulatory treatment. Therefore, the safety of these treatment modalities, especially biologic agents, during the COVID-19 pandemic, is among the most intriguing and frequently investigated issues. In a study by Damiani et al[16] in which 1193 psoriatic patients undergoing biologic agent and small molecule treatment are evaluated, it was shown that patients using biologics (tumor necrosis factor-alpha (TNF-alpha) inhibitors, interleukin (IL)-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors) have higher risk to get a positive RT-PCR test result for COVID-19, to be self-quarantined and hospitalized. However, in this study, it is also found that biologics do not increase the risk of ICU admission or mortality.[16] On the other hand, some biologics such as TNF-alpha inhibitors are associated with moderate to severe respiratory tract infections.[17]

The anti-IgE humanized antibody, omalizumab, is being widely used on-label for the treatment of severe allergic asthma, and CSU. Patients unresponsive to the first-line treatment with oral histamines up to fourfold are recommended to have 300 mg subcutaneous omalizumab every 4 weeks even though the licensed doses may vary between different countries.[1] However, the dose may be increased up to 450 or 600 mg in recalcitrant cases or partially responsive cases to the standard dose regimen.[18] Omalizumab has been shown to greatly decrease the nasal mucosal inflammation, improve nasal respiratory functions in patients with chronic rhinosinusitis.[19] The mechanisms of action which are associated with its utility in various allergic, hyperinflammatory diseases, are not only limited to binding free IgE and preventing the activation of FcεRI via its interaction with IgE.[7] Omalizumab is also shown to augment antiviral responses via several ways.[20] Firstly, plasmacytoid dendritic cells are shown to express high levels of FcεRI, the binding of specific antigens to these receptors results in the inhibition of interferon-alpha secretion which is crucial to initiate the immunity against viruses.[11] Thus, the blockage of FcεRI results in enhanced interferon-alpha secretion, propagating the antiviral responses.[11] Secondly, the allergic stimulation initiated by IgE, hampers the regulation of proteins necessary for the delivery of antigens, thus T lymphocyte activation and T-helper 1-associated viral responses are impaired.[21]

COVID-19 disease is staged into three phases: early infection, pulmonary phase, and hyperinflammation phase.[22] In the early infection phase, mild constitutional symptoms, fever, dry cough, and lymphopenia are observed; this phase is considered as the viral response phase and antiviral treatment could be initiated at this phase.[22] During the early infection phase, the inhibition of pro-inflammatory cytokines which play a pivotal role in the propagation of antiviral response, may have unfavorable results.[22] That is why biologic agents are suggested to suspend during the initial phase. In the hyperinflammatory phase, the levels of TNF-alpha, IL-2, IL-6, IL-8, and IL-1 are significantly increased, further facilitating the progression of COVID-19 and systemic organ involvement.[16,22] During this stage, selective inhibition of cytokines may be beneficial by preventing the hyperinflammation. IgE elevates the levels of heparin, various cytokines, and histamine; leading to systemic reactions such as fever, vasodilatation, itching, flushing, and allergic diseases including asthma.[21] Therefore, inhibition of IgE is most likely to result in a significant decrease in the levels of hyperinflammatory cytokines which are actively produced in the setting of COVID-19 infection. Furthermore, anti-IgE omalizumab is shown to annihilate asthma exacerbations which are mostly related to Rhinovirus.[10,23] Therefore, omalizumab may be helpful in inducing the clinical remission in COVID-19 patients.[24]

The results of our study suggest that gender, the presence of any other systemic disease and the given treatment (grouped as only omalizumab, only oral antihistamines, and both omalizumab and oral antihistamines) do not increase the risk of testing positive for COVID-19. No statistically significant relationship was determined between COVID-19 RT-PCR results and different types of treatment being used for chronic urticaria when the patients are divided into omalizumab, omalizumab along with oral antihistamines and only oral antihistamines groups ($p = 0.150$). Furthermore, only 2 cases who tested positive for COVID-19 RT-PCR, were hospitalized, the others had only mildly symptomatic disease. Our results are in concordance with the outcomes of a recent study by Kocaturk et al,[25] which concluded that patients with CSU are not at a high risk for severe COVID-19. In this study, 24 out of 27 patients with COVID-19 who were on omalizumab ± oral antihistamine treatment had mild COVID-19 and only two patients needed hospitalization.[25] On the other hand, none of the thirty-five patients who were solely on oral antihistamine treatment were hospitalized.[25] Similarly, Ayhan et al[26] reported three cases of CSU who had COVID-19, under omalizumab therapy but none of the patients presented with severe systemic symptoms which require hospital admission. In our study, we also found statistically significant

relationships between COVID-19 RT-PCR positivity vs the presence of COVID-19 symptoms ($p = 0.003$) and COVID-19 RT-PCR positivity and between the history of close contact to someone with a confirmed COVID-19 diagnosis ($p = 0.006$). However, of 125 patients who had COVID-19-related symptoms, only 107 (85.6%) were tested for COVID-19 and of 130 patients who had a history of close contact to someone with COVID-19, 108 (83.1%) patients had RT-PCT test. Therefore, it is likely that we might have missed some COVID-19 RT-PCR positive cases which limits our data. Furthermore, binary logistic regression analyses showed that being at a age >45 years was shown to increased the risk of getting a positive COVID19 RT-PCR 3.619 fold (OR, 3.619; 95% confidence interval, 1.076–12.175; $p = 0.038$). In a study by Aldhaeefi et al,[27] it is found that age >70 years, chronic kidney disease, hypertension, hyperlipidemia, and coronary artery disease are associated with persistent PCR positivity for more than 4 weeks. The associated risk factors for mortality in COVID-19 patients are found to be age ≥50 years, the presence of comorbidities such as kidney disease, cardiovascular disease, cerebrovascular disease, and hypertension in a meta-analysis by Biswas et al.[28] Conversely, we did not find any relationship COVID-19 RT-PCR results and the presence of previous malignancy, respiratory diseases, cardiovascular diseases, endocrine disorders, and rheumatologic disorders ($p > 0.05$).

In conclusion, we would like to highlight that omalizumab treatment does not seem to increase the risk for COVID-19 infection and could be safely in patients with CSU, compatible with the data in the literature. In patients with a confirmed diagnosis of COVID-19, omalizumab should be suspended until the infection is completely over. Our study has some limitations since no control group was present and only CSU patients treated in our center were included. Prospective, randomized controlled studies are needed to further support our findings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

Ethics committee approval was obtained.

IRB APPROVAL STATEMENT

Approved by the local ethics committee with the date, the project number, the decision number: 4.5.2021, GO 21/604, 2021/10-23.

AUTHOR CONTRIBUTIONS

Ecem Bostan: Conceptualization; visualization; and writing-original draft. Fethi Zaid: Conceptualization and data curation. Aysen Karaduman: Conceptualization; data curation; supervision; and editing. Sibel Dogan: Conceptualization; data curation; supervision; and editing. Duygu Gulseren, Basak Yalici-Armagan, Neslihan Akdogan, Sibel Ersoy-Evans, and Gonca Elcin: Data curation and supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [Ecem Bostan], upon reasonable request.

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SUPPORTING INFORMATION

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