ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Omalizumab as urticaria treatment in the context of the COVID-19 pandemic

O omalizumabe no tratamento da urticária no contexto da pandemia de COVID-19

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ABSTRACT

The beginning of the COVID-19 pandemic was marked by uncertainty due to lack of knowledge about the disease. Questions were raised about the use of immunobiologicals in the pandemic context, including omalizumab for patients with chronic urticaria (UC). This study assessed COVID-19 severity and the clinical course of urticaria in Brazilian patients on omalizumab therapy who were monitored by specialists. We retrospectively analyzed data from chronic urticaria patients treated with omalizumab between July, 2020 and June, 2021 who presented with COVID-19. Clinical characteristics and the course of urticaria during SARS-CoV2 infection were analyzed. The sample consisted of 28 patients treated with omalizumab, 27 of whom had chronic spontaneous urticaria (UCE) and 25% of whom had associated chronic inducible urticaria. Most of the patients (71%) were using quadruple doses of second-generation antihistamines associated with omalizumab. The symptoms of all patients were controlled. The most frequent symptoms during COVID-19 were: fever (43%), headache (36%), malaise (32%), hypo/anosmia (29%) and cough (21%). Four patients were hospitalized, including 1 in intensive care. One patient reported worsening chronic urticaria

RESUMO

O início da pandemia de COVID-19 foi marcado por incertezas diante do desconhecimento sobre a doença. Uma série de dúvidas relacionadas ao uso de imunobiológicos no contexto da pandemia foi levantada, inclusive em relação ao tratamento com omalizumabe em pacientes com urticária crônica (UC). Este estudo teve como objetivo analisar os dados relacionados à gravidade da COVID-19 e a evolução da urticária em pacientes em terapia com omalizumabe acompanhados por especialistas no Brasil. Foi realizada análise retrospectiva de dados de pacientes com UC tratados com omalizumabe entre julho/2020 e junho/2021 que apresentaram COVID-19. Foram avaliados dados relacionados às características clínicas dos pacientes e evolução da urticária durante a infecção pelo SARS-CoV2. Foram incluídos 28 pacientes em tratamento com omalizumabe, sendo 27 com urticária crônica espontânea (UCE), dos quais 25% tinham alguma urticária induzida associada. A maior parte dos pacientes (71%) estavam utilizando doses quadruplicadas de anti-histamínicos modernos de 2ª geração associados ao omalizumabe. Todos os pacientes estavam com os sintomas controlados. Entre os sintomas apresentados durante a COVID-19, os mais frequentes foram: febre (43%), ce-

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symptoms while infected with COVID-19. Five (18%) patients experienced worsening chronic urticaria symptoms after recovery from COVID-19. All patients recovered from COVID-19 without serious sequelae. Omalizumab did not appear to increase the risk of severe COVID-19 and can be safely used in patients with chronic urticaria.

Keywords: Urticaria, omalizumab, COVID-19.

faleia (36%), mal-estar (32%), hipo/anosmia (29%) e tosse (21%). Quatro pacientes foram hospitalizados, um deles em unidade de terapia intensiva. Um paciente relatou piora dos sintomas da UC durante a COVID-19. Cinco (18%) pacientes apresentaram piora dos sintomas da UC após a resolução da COVID-19. Todos os pacientes se recuperaram da COVID-19 sem sequelas graves. O OMA não pareceu aumentar o risco de COVID-19 grave e poderia ser usado com segurança em pacientes com UC.

Descritores: Urticária, omalizumab, COVID-19.

COVID-19, the disease caused by SARS-CoV-2 coronavirus, was first described in 2019. Its main manifestations were fever, flu-like symptoms, pneumonia, severe acute respiratory syndrome, diarrhea, and hyposmia, indicating its systemic nature.[1] On March 11, 2020, the World Health Organization declared COVID-19 a pandemic.[2] At that point, when both the virus and the disease were still little known and the number of deaths was progressively increasing, questions were raised about populations at greater risk for serious illness, such as immunosuppressed patients and those with chronic pathologies and severe comorbidities.[3] Among immunologists, one of the most pressing questions was whether immunobiologicals would affect the course of COVID-19, putting patients undergoing immunobiological treatment at greater risk for more severe COVID-19.[4]

Chronic urticaria (CU) significantly impacts the quality of life of poorly controlled patients. About 40% of cases do not respond to antihistamines and are indicated for omalizumab (OMA), an anti-IgE antibody considered the first treatment option for these patients.[5,6]

It has been demonstrated that OMA treatment can restore interferon-alpha-mediated response to both rhinovirus and influenza by reducing expression of high-affinity IgE receptors on the surface of cells, including mast cells, basophils, and plasmacytoid dendritic cells, which suggests that OMA has an antiviral role.[7-9] Thus, theoretically, OMA treatment should not be suspended in patients with mild to moderate COVID-19. However, at the beginning of the pandemic, most experts recommended that in patients with severe COVID-19, OMA should be suspended until at least 2 weeks after recovery.[4]

Due to the limited information and uncertainty about OMA use during acute SARS-CoV-2 infection, we analyzed data on COVID-19 severity and the course of urticaria in patients followed by specialists in Brazil.

Methods

This retrospective study analyzed the medical records of CU patients undergoing OMA treatment who had a confirmed or highly suspected SARS-CoV-2 infection between July 2020 and June 2021. Infections were considered confirmed after positive COVID-19 test results (RT-PCR, rapid immunodiagnostic test, and IgM and/or IgG serology) or highly suspected when there was a strongly suggestive epidemiological history associated with flu-like symptoms.

The following data were collected from the medical records of each patient: sex, age, CU subtype, time since CU onset, urticaria treatment at the time of SARS-CoV-2 infection, COVID-19 symptoms, hospitalization for COVID-19, the use of nonsteroidal anti-inflammatory drugs, and the course of urticaria after COVID-19.

Patient and SARS-CoV-2 infection data are described below.

Results

We included 28 patients undergoing OMA treatment (79% female) who were diagnosed with COVID-19 according to the above-mentioned criteria. The mean patient age was 38.5 (SD, 10) years. Almost all patients had been diagnosed with CSU. Among these, seven (25%) had some associated

chronic inducible urticaria: dermographism (3), solar urticaria (3), or delayed pressure urticaria (1). Only 1 patient had isolated chronic inducible urticaria (solar urticaria). The mean duration of urticaria was 7.6 (range, 1.3-26) years. Most patients (71%) were using a quadruple dose of modern second generation antihistamines associated with OMA, and 8 patients (29%) were on OMA monotherapy. The symptoms of all patients were controlled (urticaria control test score ≥ 12 or urticaria activity score over 7 days ≤ 6) prior to SARS-CoV-2 infection.

COVID-19 diagnosis was confirmed by RT-PCR in 18 patients; 4 (14%) had positive IgM and/or IgG serology for SARS-CoV-2; 3 (11%) had positive results in a rapid immunodiagnostic test for SARS-CoV-2. Three presented highly suggestive symptoms after contact with COVID-19 patients during the pandemic. The most frequently observed symptoms were fever (43%), headache (36%), malaise (32%), hyposmia/anosmia (29%), cough (21%), dyspnea (11%), and dysgeusia (7%). Four patients were hospitalized, one in the intensive care unit. Seven patients were treated with nonsteroidal anti-inflammatory drugs, which had no direct impact on urticaria control. One patient reported worsening CU symptoms while infected. Five (18%) experienced worsening CU symptoms after recovering from COVID-19 (Table 1). All patients recovered from COVID-19 without serious sequelae.

Discussion

CU treatment aims at complete symptom control, and OMA therapy can control the disease in up to 85% of patients.[6,10] Viral infections are a frequent cause of acute urticaria and can be an exacerbating factor in chronic urticaria.[11] SARS-CoV-2 infection has also been associated with manifestations of acute urticaria, with an incidence between 1.9% and 3.4%.[1,12] A Turkish study found no significant association between positive RT-PCR for SARS-CoV-2 and treatment type (antihistamines, OMA, or both) in a subgroup of 15 patients with CSU who presented COVID-19-related symptoms, suggesting that OMA treatment does not predispose to or prevent SARS-CoV-2 infection.[13]

Our data suggest that patients whose symptoms have been controlled through OMA have a low risk of exacerbated CSU during SARS-CoV-2 infection. However, most studies have shown that urticaria appears after COVID-19 symptom onset.[1] Interestingly, 5 patients reported worsening symptoms after recovering from COVID-19, even though their urticaria treatment remained unchanged. Mutean et al. reported that 44% of patients with CSU and COVID-19 experience worsening urticaria during infection, especially those with moderate to severe COVID-19.[14] Passante et al. observed no CSU exacerbation in their series of 7 patients who were being treated with OMA and tested positive for COVID-19 but had mild or no symptoms.[15] OMA controls urticaria symptoms by reducing mast cell activation and releasing mast cell mediators. It is possible that the antiviral effects of OMA could dampen infection and inflammation in mild cases of COVID-19, preventing urticaria from worsening. However, OMA may be insufficient to overcome the effects of more severe infection, which can trigger or worsen urticaria symptoms.

Our data also suggest that OMA treatment does not increase the risk of severe COVID-19. However, 4 of the patients who tested positive for COVID-19 were hospitalized, indicating moderate to severe illness. A retrospective analysis of patients from Romania with CSU found that 71% of patients with CSU and SARS-CoV-2 infection had moderate to severe COVID-19, but that treatment with OMA was not associated with COVID-19 severity.[14] Kocatürk et al. reported that 90% of patients with COVID-19 who were being treated with OMA +/- antihistamines had mild COVID-19, and only 2 patients required hospitalization.[16] Ayhan et al. reported on 3 CSU patients treated with OMA who had mild COVID-19.[17] Paulino et al. also reported on a CSU patient treated with OMA whose only symptoms during SARS-CoV-2 infection were anosmia and arthralgia.[18] Overall, current data suggest that OMA treatment in patients with CU is not a risk factor for more severe COVID-19.

In conclusion, our results suggest that most patients can continue OMA therapy despite SARS-CoV-2 infection. OMA did not appear to increase the risk of severe COVID-19 and could be safely used in patients with CU. However, further studies are needed with larger patient samples to more conclusively recommend continued use of OMA in CU patients with COVID-19.

Table 1
Clinical characteristics of the patients

Patient ID	Sex	Age (y)	CU subtypes	COVID test results	CU treatment (besides OMA)	Months from CU onset to COVID-19	Months since beginning OMA treatment	Hospitalized for COVID-19
1	M	33	CSU	SARS-CoV2 rapid immunodiagnostic test	Second generation anti-H1 (4X)	204	16	No
2	F	47	CSU, delayed pressure urticaria	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (2X)	114	24	No
3	F	43	CSU	RT-PCR	None	60	48	No
4	F	36	CSU	RT-PCR	None	72	68	No
5	F	41	CSU	RT-PCR	Second generation anti-H1 (4X)	24	Unknown	No
6	F	57	CSU, dermographism	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (on demand)	36	26	No
7	M	46	CSU, dermographism	RT-PCR	Second generation anti-H1 (on demand)	60	25	No
8	F	43	CSU	RT-PCR	None	60	Unknown	No
9	F	33	CSU	RT-PCR	Second generation anti-H1 (4X)	48	33	No
10	F	40	CSU, solar urticaria	High clinical suspicion	Second generation anti-H1 (2X)	240	7	Yes
11	F	56	CSU	RT-PCR	Second generation anti-H1 (2X)	154	8	No
12	F	50	CSU	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (licensed dose)	72	60	No
13	M	31	CSU	RT-PCR	Second generation anti-H1 (2X)	60	12	No

CU = chronic urticaria, CSU = chronic spontaneous urticaria, OMA = omalizumab, RT-PCR = reverse transcriptase-polymerase chain reaction.

Table 1 *(continuation)*
Clinical characteristics of the patients

Patient ID	Sex	Age (y)	CU subtypes	COVID test results	CU treatment (besides OMA)	Months from CU onset to COVID-19	Months since beginning OMA treatment	Hospitalized for COVID-19
14	F	12	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	15	11	No
15	F	22	Solar urticaria	RT-PCR	None	36	20	No
16	F	47	CSU	IgM serology and/or IgG SARS-CoV2	Second generation anti-H1 (licensed dose)	114	24	No
17	F	34	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	84	24	No
18	F	37	CSU	RT-PCR	Second generation anti-H1 (4X)	16	0.5	No
19	M	38	CSU	RT-PCR	Second generation anti-H1 (licensed dose)	18	9	No
20	F	44	CSU	SARS-CoV2 rapid immunodiagnosis test	Second generation anti-H1 (4X)	312	28	No
21	M	47	CSU	RT-PCR	None	36	20	No
22	F	38	CSU	SARS-CoV2 rapid immunodiagnosis test	Second generation anti-H1 (4X)	41	5	No
23	F	33	CSU, dermographism	RT-PCR	Second generation anti-H1 (licensed dose)	144	50	No
24	F	38	CSU	RT-PCR	None	41	5	No
25	M	19	CSU	RT-PCR	Second generation anti-H1 (2X)	70	62	No

CU = chronic urticaria, CSU = chronic spontaneous urticaria, OMA = omalizumab, RT-PCR = reverse transcriptase-polymerase chain reaction.

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