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The course of COVID-19 in patients with chronic spontaneous urticaria receiving omalizumab treatment

L’évolution du COVID-19 chez les patients atteints d’urticaire spontanée chronique recevant un traitement par omalizumab

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A B S T R A C T

Background and aim. – Although there are case reports and guideline recommendations that states omalizumab can be used in chronic spontaneous urticaria (CSU) patients during SARS-CoV-2 pandemic, there are scarce studies showing the course of Coronavirus disease 2019 (COVID-19) in CSU patients receiving omalizumab.

Materials and methods. – A total of 370 patients with chronic urticaria were included in the study between June 2020 and December 31, 2020.

Results. – Sixty patients (16.2%) became infected with the SARS-CoV-2. The rate of pneumonia and hospitalization were 4.1% and 1.9%. There was no significant difference was determined between the CSU patients with omalizumab treatment and the non-receivers in regard to the rate of SARS-CoV-2 (+) (P: 0.567) and in regard to the rate of SARS-CoV-2 related pneumonia and hospitalization (P: 0.331 and P: 0.690). Gender, duration of CSU, serum IgE levels, omalizumab treatment, and atopy were not found to be associated with an increased risk for SARS-CoV-2 positivity in patients with CSU.

Conclusion. – Our study shows that the use of omalizumab does not increase the risk of COVID-19 infection, COVID-19-related pneumonia and COVID-19-related hospitalizations in CSU patients.

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RÉSUMÉ

Introduction. – Bien qu’il existe des rapports de cas et des recommandations de lignes directrices indiquant que l’omalizumab peut être utilisé chez les patients atteints d’urticaire spontanée chronique (CSU) pendant la pandémie de SARS-CoV-2, il existe peu d’études montrant l’évolution de la maladie à coronavirus 2019 (COVID-19) chez les patients atteints d’urticaire spontanée recevant de l’omalizumab.

Matières et méthodes. – Un total de 370 patients atteints d’urticaire chronique ont été inclus dans l’étude entre juin 2020 et le 31 décembre 2020.

Résultat. – Soixante patients (16,2 %) ont été infectés par le SARS-CoV-2. Les taux de pneumonie et d’hospitalisation étaient de 4,1 % et de 1,9 %. Aucune différence significative n’a été déterminée entre les patients atteints de CSU traités par omalizumab et les non-traités en ce qui concerne le taux de SARS-CoV-2 (+) (p: 0,567) et en ce qui concerne le taux de pneumonie et d’hospitalisation liées au SRAS-CoV-2 (p: 0,331 et p: 0,690). Le genre, la durée de la CSU, les taux sériques d’IgE, le traitement par omalizumab et l’atopie n’ont pas été associés à un risque accru de positivité au SRAS-CoV-2 chez les patients atteints de CSU.

Conclusion. – Notre étude montre que l’utilisation de l’omalizumab n’augmente pas le risque d’infection à la COVID-19, de pneumonie liée à la COVID-19 et d’hospitalisations chez les patients atteints de CSU et soutient l’opinion selon laquelle l’omalizumab peut être utilisé en toute sécurité chez les patients atteints de CSU pendant la pandémie de COVID-19.

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1. Introduction

SARS-CoV-2 was first reported in the Wuhan city of China and soon after, the virus and hence the disease got spread rapidly to the entire world and the World Health Organization (WHO) in March 2020, has declared it as a global pandemic [1]. Since there is still no definitive treatment for coronavirus disease 2019 (COVID-19) and mass immunization is not at the desired rate, it is very important to identify the most vulnerable patients and the effects of the drugs they use on the course of COVID-19 to reduce the mortality and morbidity caused by SARS-CoV-2. Additionally, the effect of chronic diseases and drugs used in treatment of these diseases on the course of COVID-19 continues to be the subject of many studies.

Omalizumab is an anti-IgE monoclonal antibody used for the treatment of chronic spontaneous urticaria (CSU) patients aged 12 years and older who are refractory to standard dose of antihistamines [2]. It has also been approved for the treatment of severe asthma patients with indoor allergen sensitivity [3]. In addition to its anti-IgE activity, omalizumab, especially in pediatric patients with allergic asthma, ameliorates inadequate antiviral response, reduces the duration of rhinovirus infection and decreases the viral shedding [4]. Therefore, it can be argued that IgE-targeting antibody treatment, omalizumab, may have protective effects against viruses like SARS-CoV-2. Although there are case reports [2,5,6] and guideline recommendations that states omalizumab can be used in CSU patients during SARS-CoV-2 pandemic, there are scarce studies showing the course of COVID-19 in CSU patients receiving omalizumab [7].

Therefore, the aims of present study were to try to expose the course of SARS-CoV-2 in patients with chronic urticaria, to compare the prevalence of SARS-CoV-2 infection, SARS-CoV-2 related pneumonia, and SARS-CoV-2 related hospitalization in patients with chronic urticaria receiving omalizumab treatment and patients who did not receive omalizumab treatment (non-receivers) and to identify possible risk factor for SARS-CoV-2 positivity in CSU patients.

2. Material and methods

Adult patients with chronic urticaria, who were being followed-up in a tertiary allergy clinic in Konya, located in the central Anatolia, Turkey, between June 2020 and December 31, 2020, were selected for the study. Forty-three patients with irregular treatment and insufficient information in their files were excluded from the study. Three hundred seventy patients who were receiving active-continuous treatment for CSU during the study period were included in the study.

Diagnosis of chronic urticaria was made by the presence of recurrent urticaria, angioedema, or both, for a period of six weeks or longer. Oral antihistamine treatments were given as the first-line treatment to the patients who applied with the complaints of urticaria. In patients who did not respond adequately, the first treatment dose was increased up to four times or a second-generation oral antihistamine from a different group to the treatment in line with the guideline recommendations [8]. Patients who did not benefit from these treatments, omalizumab, 300 mg/4 weeks/subcutaneously, was applied for 12 weeks. At the end of 12 weeks, the treatment of patients who benefited from omalizumab treatment, the treatment was completed to 24 weeks and then omalizumab treatment was stopped.

The diagnosis of SARS-CoV-2 was made by a positive Polymerase Chain Reaction (PCR) test in patients with consistent clinical presentation for COVID-19 or by consistent computed tomography findings.

Whole blood count was measured using the Abbott Cell Dyn 3700 series (Sheath reagent), and quantitative determination of serum immunoglobulin (IgE) was made by the Siemens BN II/BN ProSpec system (using particle-enhanced immunonephelometry).

The study was approved by Karatay University Ethics Committee (Decision number 2020/015).

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software package. Normally distributed parameters were presented as mean ± standard deviation and data that were not normally distributed were expressed as median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using a Chi² test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exact or Chi² tests where appropriate. As a result of these statistical analysis, parameters with P<0.2 between SARS-CoV-2 (+) patients and SARS-CoV-2 (−) patients were subjected to regression analysis. Binomial logistic regression analysis was performed to determine independent predictors for SARS-CoV-2 positivity.

3. Results

A total of 370 patients with chronic urticaria were included in the study [female: 258 (69.7%), male; 112 (30.3%)]. The mean age was 40.50 years (18 to 86 years). The mean duration of disease was 3 years (0.5–29). One hundred twenty patients (32.4%) have at least one allergen sensitivity and the rest of them were non-allergic. Seventy-nine patients (21.4%) had at least one accompanying comorbidity and the most common comorbidity was hypertension (8.4%). One hundred seventy-nine patients (48.4%) were receiving omalizumab treatment for chronic urticaria. Mean serum IgE level was 87.55 (7–3880) IU/mL, eosinophil count was 130 (0–2290) cells/mL and vitamin D level was 15.17 (2–153) μg/L.

In 23 of 27 CSU patients who were accepted as SARS-CoV-2 (+) and received omalizumab treatment, the diagnosis of SARS-CoV-2 was made by PCR test. In 26 of 33 patients who were accepted as SARS-CoV-2 (+) and did not receive omalizumab treatment, the diagnosis of SARS-CoV-2 was made by PCR test. Sixty patients (16.2%) became infected with the SARS-CoV-2 virus during the study period. Fifteen patients (4.1%) had pneumonia due to SARS-CoV-2 and seven of them (1.9%) were hospitalized. Clinical characteristics of the patients are summarized in Table 1.

We divided the study participants into two group as the chronic urticaria patients on omalizumab treatment and chronic urticaria patients not receiving omalizumab treatment; no significant difference was determined between the groups in terms of age, gender, duration of disease, accompanying comorbidities (Type 2 diabetes mellitus [DM], hypertension [HT], and coronary artery disease [CAD]), baseline eosinophil count and vitamin D level and frequency of infection with SARS-CoV-2 virus. SARS-CoV-2 related pneumonia and SARS-CoV-2 related hospitalization. However, there was a significant difference between the groups in terms of sensitivity to allergens (atopy) and serum IgE levels (P: 0.027 and P: 0.001, respectively).

Within the 370 patients included in the study, the rate of pneumonia was 4.1% (15 patients). Twenty-seven patients (15.1%) in omalizumab group and 33 patients (17.3%) in non omalizumab group became infected with the SARS-CoV-2 virus during the study period. There was no significant difference was determined between the chronic urticaria patients with omalizumab treatment and the non-receivers in regard to the rate of SARS-CoV-2 (+) (P: 0.567).

Nine patients (5%) in omalizumab group and six patients (3.1%) in non-omalizumab group had pneumonia due to SARS-CoV-2. Four patients (2.2%) in omalizumab group and three patients (1.5%) in
Table 1
Demographic, clinical and laboratory parameters of patients with CSU according to omalizumab treatment.

| Parameters          | Study population n: 370 | Chronic urticaria patients with omalizumab (n: 179) | Chronic urticaria patients with out omalizumab (n: 191) | P       |
|---------------------|-------------------------|--------------------------------------------------|-----------------------------------------------------|---------|
| Age, years          | 40.50 (18–86)           | 42 (18–83)                                       | 38 (18–86)                                         | 0.201   |
| Gender, female, n (%)| 258 (69.7)              | 118 (65.9)                                       | 140 (73.3)                                         | 0.123   |
| Duration of disease, years | 3 (0.5–29)           | 3 (0.5–20)                                       | 3 (0.6–29)                                         | 0.714   |
| Atopy, n (%)        | 120 (32.4)              | 68 (38)                                          | 52 (27.2)                                          | 0.027   |
| Comorbidities, n %  | 79 (21.4)               | 45 (25.1)                                        | 34 (17.8)                                          | 0.085   |
| Hypertension        | 22 (5.9)                | 15 (8.4)                                         | 7 (3.7)                                            | 0.055   |
| Type 2 DM           | 16 (4.3)                | 8 (4.5)                                          | 8 (4.2)                                            | 0.894   |
| CAD                 | 13 (3.5)                | 6 (3.4)                                          | 7 (3.7)                                            | 0.870   |
| IgE, at diagnosis, IU/mL | 87.55 (7–3880)       | 106 (10.8–3880)                                  | 81 (7–2500)                                        | 0.001   |
| Vitamin D, µg/L     | 15.17 (2–153)           | 15.35 (2–153)                                    | 12.40 (10.1–97)                                   | 0.871   |
| Eosinophil count, cell/mL | 130 (0–2250)      | 120 (0–1850)                                     | 140 (1.10–2290)                                   | 0.098   |
| SARS-CoV-2, n (%)   | 60 (16.2)               | 27 (15.1)                                        | 33 (17.3)                                          | 0.567   |
| Pneumonia, n (%)    | 15 (4.1)                | 9 (5)                                            | 6 (3.1)                                            | 0.331   |
| Hospitalization, n (%) | 7 (1.9)                | 4 (2.2)                                          | 3 (1.5)                                            | 0.690   |

CSU: chronic spontaneous urticaria; DM: diabetes mellitus; CAD: coronary artery disease; Ig: immunoglobulin; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 2
Demographic and clinical characteristics of patients with CSU according to SARS-CoV-2.

| Parameters          | SARS-CoV-2 (+) (n: 60) | SARS-CoV-2 (-) (n: 310) | P       |
|---------------------|------------------------|-------------------------|---------|
| Age, years          | 45.5 (19–83)           | 41.50 (18–83)           | 0.453   |
| Gender, female, n (%)| 40 (66.7)              | 218 (70.3)              | 0.573   |
| Duration of disease, years | 2.5 (0.6–20)      | 3 (0.5–29)              | 0.417   |
| Atopy, n (%)        | 17 (28.3)              | 103 (33.2)              | 0.459   |
| Omalizumab treatment, n (%) | 27 (45)              | 152 (49.0)              | 0.567   |
| Comorbidities, n (%) | 12 (20)                | 67 (21.6)               | 0.780   |
| Hypertension        | 4 (6.7)                | 12 (3.9)                | 0.330   |
| Type 2 DM           | 3 (5)                  | 19 (6.1)                | 0.735   |
| CAD                 | 2 (3.3)                | 11 (3.5)                | 0.934   |
| IgE, at diagnosis, IU/mL | 103 (16–2580)         | 119 (10–3880)           | 0.876   |
| Eosinophil count, cell/mL | 160 (0–1850)         | 120 (0–1390)            | 0.015   |
| Vitamin D, µg/L     | 15.14 (6.3–45)         | 15.23 (2–153)           | 0.988   |

CSU: chronic spontaneous urticaria; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; DM: diabetes mellitus; CAD: coronary artery disease; Ig: immunoglobulin.

non-omalizumab group were hospitalized. There was no significant difference was determined between the chronic urticaria patients with omalizumab treatment and the non-receivers in regard to the rate of SARS-CoV-2 related pneumonia and SARS-CoV-2 related hospitalization (P: 0.331 and P: 0.690) (Table 1). There were no patients admitted to the intensive care unit during the study period. We did not lost any of our patients due to COVID-19 infection.

When SARS-CoV-2 positive and negative CSU patients were compared; there were no significant differences between both groups in terms of gender, current age, duration of disease, accompanying comorbidities, serum IgE levels, vitamin D levels and rate of patients receiving omalizumab therapy. A significant difference was determined in terms of eosinophil count (P: 0.015) (Table 2).

Univariate and multivariant binary logistic regression analyses showed that, current age, gender, duration of disease, the accompanying comorbidities, eosinophil count, serum IgE levels, omalizumab treatment, and atopy were not found to be associated with an increased risk for SARS-CoV-2 positivity in patients with CSU (Table 3).

4. Discussion

The presented study had three clinically important findings. Firstly, patients with chronic urticaria receiving omalizumab had higher atopy rates and serum IgE values than patients with chronic urticaria who did not receive omalizumab. Secondly, the prevalence of SARS-CoV-2, SARS-CoV-2 associated pneumonia, and SARS-CoV-2 related hospitalization rates are similar in chronic urticaria patients receiving omalizumab and chronic urticaria patients not receiving omalizumab. Lastly, age, gender, presence of atopy, duration of CSU or use of omalizumab are not a risk factor for SARS-CoV-2 positivity (+) in patients with chronic urticaria.

In our study, atopy rates and serum IgE values were higher in chronic urticaria patients who received omalizumab than in chronic urticaria patients who did not receive omalizumab. Almost 50% of CSU patients have elevated IgE levels. It has been demonstrated that elevated IgE levels in CSU patients are associated with increased disease activity, longer disease duration and rapid response to omalizumab [9]. Given that the Omalizumab is second line treatment for patients who have inadequate response to antihistamine treatments, elevated IgE levels in patients receiving omalizumab are not surprising. Allergic skin diseases like atopic dermatitis and urticaria are closely associated comorbidities with allergic rhinitis and rhinosinusitis. Chronic urticaria is the most common comorbid disease in patients with atopic dermatitis and it has been shown that the risk of CSU is 2.5 times higher in patients with atopic dermatitis [10]. High rates of co-existence of allergic diseases appears to be associated with common and/or similar pathological pathways. For this reason, we think that CSU patients receiving omalizumab have a higher rate of atopy.

In our study, we found that prevalence of SARS-CoV-2, SARS-CoV-2 associated pneumonia and SARS-CoV-2 related hospitalization rates are similar in patients with chronic urticaria who received omalizumab or did not receive omalizumab. Abduelmula et al. reported that none of the 184 CSU and asthma patients who received omalizumab were tested positive for SARS-CoV-2 [11]. In another study, Bostan et al. reported that 15 (9.6%) of the 233 patients with CSU were tested positive for SARS-CoV-2 and 2 patients were hospitalized due to SARS-CoV-2 disease [12]. Kocatekar et al. also reported that 11 (13.9%) of the 79 patients with CSU who had SARS-CoV-2 positivity 11 patients (13.9%) were hospitalized (8 mild disease and 3 severe disease) [13]. In our study, the prevalence of SARS-CoV-2 was 16.2% and the hospitalization rate was 1.9%, which is similar to the aforementioned studies.

Ayan et al. reported that 3 patients with COVID-19 who were receiving omalizumab, one patient was hospitalized for SARS-CoV-2 related pneumonia, one patient was followed at home due to SARS-CoV-2 related mild pneumonia without being hospitalized, and lung involvement did not develop in the last patient. All three patients recovered from COVID-19 with relatively mild disease [6]. Kocatekar et al. reported that of the 70 COVID 19 (+) CSU patients
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CSU: chronic spontaneous urticaria; IgG: immunoglobulin.

Disclosure of interest

The authors declare that they have no competing interest.

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