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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

The global impact of the COVID-19 pandemic on the management and course of chronic urticaria

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Abstract

Introduction: The COVID-19 pandemic dramatically disrupts health care around the globe. The impact of the pandemic on chronic urticaria (CU) and its management are largely unknown.

Aim: To understand how CU patients are affected by the COVID-19 pandemic; how specialists alter CU patient management; and the course of CU in patients with COVID-19.

Materials and Methods: Our cross-sectional, international, questionnaire-based, multicenter UCARE COVID-CU study assessed the impact of the pandemic on patient consultations, remote treatment, changes in medications, and clinical consequences.

Results: The COVID-19 pandemic severely impairs CU patient care, with less than 50% of the weekly numbers of patients treated as compared to before the pandemic. Reduced patient referrals and clinic hours were the major reasons. Almost half of responding UCARE physicians were involved in COVID-19 patient care, which negatively impacted on the care of urticaria patients. The rate of face-to-face consultations decreased by 62%, from 90% to less than half, whereas the rate of remote consultations increased by more than 600%, from one in 10 to more than two thirds. Cyclosporine and systemic corticosteroids, but not antihistamines or omalizumab, are used less during the pandemic. CU does not affect the course of COVID-19, but COVID-19 results in CU exacerbation in one of three patients, with higher rates in patients with severe COVID-19.

Conclusions: The COVID-19 pandemic brings major changes and challenges for CU patients and their physicians. The long-term consequences of these changes, especially the increased use of remote consultations, require careful evaluation.

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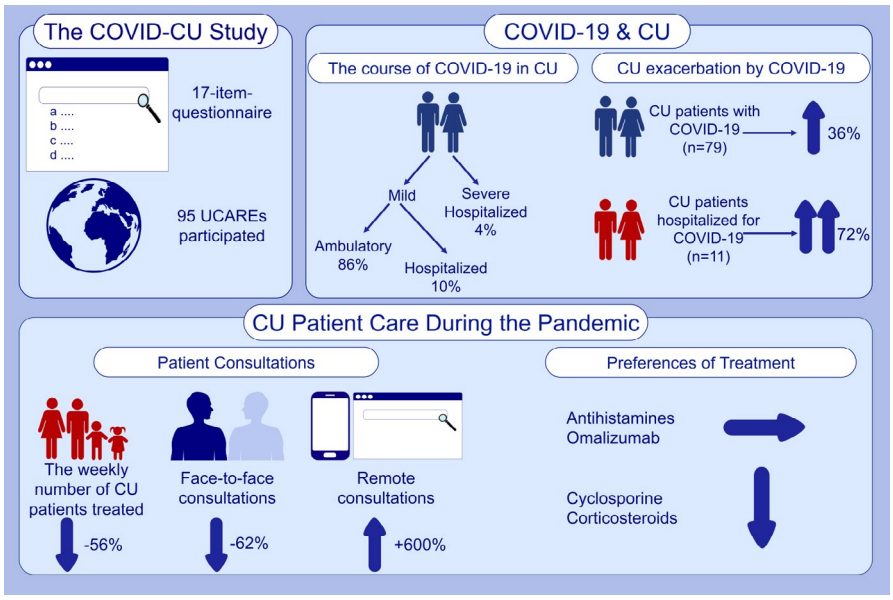
KEYWORDS
chronic urticaria, COVID-19, cyclosporine, omalizumab, pandemic, SARS-CoV-2, treatment, UCARE



GRAPHICAL ABSTRACT

The COVID-19 pandemic severely impairs CU patient care, weekly number of patients decreased by more than 50%, and the rate of face-to-face consultations decreased by 62%. CU does not affect the course of COVID-19 with only 4% of CU patients having a severe course of COVID-19, but COVID-19 results in CU exacerbation in one of three patients, with higher rates in patients with severe COVID-19. Cyclosporine and systemic corticosteroids, but not antihistamines or omalizumab, are used less during the pandemic.
Abbreviations: CU, chronic urticarial; COVID-19, coronavirus disease 2019; UCARE: urticaria centers of reference and excellence.

1 | INTRODUCTION

Chronic urticaria (CU) is a common disease with more than 50 million patients affected globally.[1] The main effector cells of CU are skin mast cells, often activated by autoimmune mechanisms. This results in the release of histamine and other mediators with subsequent sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment.[2] The first-line treatment of CU is second-generation H1 antihistamines, which provide complete control in less than 50% of the patients, even at up to fourfold doses.[3,4] In antihistamine-resistant patients, treatment with omalizumab and—if this fails—cyclosporine is the current guideline-recommended therapy of choice.[5]

Since the first months of 2020, severe acute respiratory coronavirus 2 (SARS-CoV-2) has spread rapidly across the globe causing the "coronavirus disease 2019" (COVID-19) pandemic, the worst global public health crisis since the influenza pandemic more than a hundred years ago. As of now, more than 30 million patients have been diagnosed with COVID-19 around the world, with more than 900,000 deaths in 188 countries.[6] SARS-CoV-2 leads to an upregulated immune response in the monocytic macrophage system, which may produce a severe inflammatory systemic state, hypercoagulative milieu, and damage in lungs as well as other internal organs, the hematological system, gastrointestinal tract, kidneys, and central nervous system.[7]

The COVID-19 pandemic dramatically affects healthcare systems and patient care. Patients with CU and their treating physicians are affected by social distancing measures, lockdowns, travel restrictions, and changes in management patterns due to the risk of infection with SARS-CoV-2. CU is a common and often severe disease. A significant number of CU patients are being cared for by expert physicians at hospital-based urticaria centers of reference and excellence (UCAREs).[8] The COVID-19 pandemic prompted frequent queries to UCAREs from both CU patients and CU treating physicians, especially on the treatment of urticaria with biologics and immunosuppressive treatment. The most common questions of concerns are whether treatment of CU might affect the course of COVID-19, whether the treatments or the disease itself make CU patients more prone to contract COVID-19 or to result in severe COVID-19, whether COVID-19 aggravates CU, whether the patients can be managed by remote consultations, and whether involvement of physicians in COVID-19 care will impair urticaria care. As of now, these questions remain unanswered.

Recently, several scientific societies have issued expert-led practical recommendations on the management of patients with dermatologic or allergic diseases with type 2 inflammation including urticaria during the COVID-19 pandemic. These recommendations are based on expert experience and consensus, rather than evidence from controlled studies. They aim to ensure patient and healthcare worker

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safety, and they provide guidance on the use of treatments including biologics and immunosuppressive treatments.[9-11] For instance, the position paper from German Allergologists and European Academy of Allergy and Clinical Immunology (EAACI) recommends that treatment of urticaria with omalizumab in patients with mild-to-moderate COVID-19, or when SARS-CoV-2 infection is suspected, is to be continued if supported by a patient-based risk-benefit analysis and patient consent. In patients with severe COVID-19, omalizumab injection interval prolongation or treatment interruption should be considered, taking into account the risk of the possible requirement of systemic glucocorticoids.[11] If and how these recommendations are implemented is currently unknown.

The pathogenesis of severe COVID-19 is characterized by elevated levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and chemokine (C-C-motif) ligand 2 (CCL2),[12] many of which are produced and released by mast cells. Indeed, SARS-CoV-2 activates mast cells,[13] the key effector cells in CU, as well as other immune cells such as basophils, neutrophils, monocytes/macrophages, and natural killer cells, and leads to cytokine storm.[14] Mast cells can recognize and respond to viruses through several different receptors, including Toll-like receptors, retinoic acid–inducible gene-I–like receptors, FcεRI, complement, and IL-1 receptors. Engagement of these receptors results in mast cell activation and degranulation, the *de novo* synthesis of eicosanoids as well as numerous cytokines, chemokines, and growth factors.[15] Activation of mast cells in response to viral infection may have protective effects by helping the immune system or directly fighting the infection. However, worsening of inflammation and severe disease may occur in case of extensive mast cell activation with increased levels of inflammatory cytokine and chemokine release.[12] Basophils are also involved in the pathogenesis of COVID-19 and CU. Basophil numbers are reduced in patients with COVID-19 and levels return to normal upon remission, similar to chronic spontaneous urticaria, where high disease activity is linked to basopenia and effective treatment results in normalization of blood basophil numbers.[16] These effects may explain why there are several reports of urticaria and angioedema associated with COVID-19 infection in the literature, and urticaria-like lesions were ranked as the second most common cutaneous manifestation of COVID-19 infection and reported to be present in 19% of patients in a series from Spain.[17] Also, COVID-19 can lead to exacerbation of CU.[18] How often this happens remains unknown.

With the aim of learning from the experience of urticaria specialists at UCAREs worldwide, we designed the COVID-CU study to understand how CU patients, their treatment, and course of disease are affected by the COVID-19 pandemic. The focus of COVID-CU is to characterize the changes that the pandemic has brought for the work of UCARE physicians who managed their CU patients during the pandemic.

TABLE 1 Demographic characteristics of responding UCARE physicians (*n* = 95)

Characteristics		% (n)
Specialty[a]	Allergy-immunology	62.2 (59)
	Dermatology	53.7 (51)
	Pediatric allergy	3.2 (3)
	Internal medicine	2.1 (2)
Practice type[a]	University hospital	81.2 (77)
	Private clinic	24.3 (23)
	Public hospital	18 (17)
Location of UCARE	Europe	55.8 (53)
	Asia	18.9 (18)
	South America	18.9 (18)
	North America	4.2 (4)
	Africa	1.1 (1)
	Australia/Oceania	1.1 (1)

[a]More than one answer was possible.

2 | MATERIALS AND METHODS

The COVID-CU study is a cross-sectional, international, multicenter study, in which a 17-item questionnaire was distributed to all member centers of the UCARE network (see Appendix-1 for the questionnaire) (total 110 centers; https://www.ga2len-ucare.com/centers.html).[8]

The demographic characteristics of the participating centers are given in Table 1.

COVID-19 disease severity was defined by using the scale provided by World Health Organization.[19]

2.1 | Questionnaire design

The questionnaire was developed by the steering committee members of the COVID-CU study (Emek Kocatürk, Andaç Salman, Jonny Peter, Ivan Cherrez-Ojeda, Paulo Criado, and Marcus Maurer) to query the most prevalent issues that urticaria specialists experience during the COVID-19 pandemic around the world. The focus and selection of questions were based on the evolving clinical experience with the impact of the pandemic on the management of patients and its impact on UCARE physicians and patients, as well as on patient and physician queries. The final version of the survey was approved by all COVID-CU steering committee members. The questionnaire comprised of 17 questions, focused on the impact of the pandemic on patient consultations, the implementation of measures for remote treatment, changes in the use of medications, and the course of COVID-19 in patients with CU.

2.2 | Questionnaire implementation

The questionnaire was pilot tested by 10 UCAREs before distribution and checked for ease of comprehension. The accuracy and

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completeness of the responses were reviewed by the steering committee prior to wider distribution. The survey included a combination of fill-in-the-blank and multiple-choice questions.

2.3 | Questionnaire distribution

Questionnaires were distributed through the UCARE email link to UCARE centers between July 28 and September 1. Three reminders with one-week intervals were sent.

2.4 | Questionnaire response rate and respondents

Of a total of 110 UCAREs, 95 responded to the questionnaire (response rate 86.4%). The majority of the respondents were from UCAREs at allergy-immunology departments (41.1%), were practising at university hospitals (61.1%), and were located in Europe (55.8%). Characteristics of the respondents are presented in Table 1.

2.5 | Data analysis

Quality control of the questionnaire responses was performed. Data were summarized as mean ±standard deviation and median (min.-max.) for continuous variables and frequencies (percentiles) for categorical variables. The Student t test or the Mann-Whitney U test was used for independent group comparisons, depending on the distributional properties of the data. The paired-samples *t* test was used for the comparison of means in two related groups. The chi-square test was used for proportions, and its counterpart Fisher's exact test was used when the data were sparse. Univariate logistic regression analysis was also performed to examine risk factors for different dependent variables. All analyses were performed by IBM SPSS Statistics for Windows, Version 20.0. A *P* value <0.05 was considered as statistically significant.

3 | RESULTS

3.1 | The COVID-19 pandemic severely impairs CU patient care

During the COVID-19 pandemic, the weekly number of CU patients treated at UCAREs decreased by more than 50% (mean ±SD: 56.6 ± 25.8%; median: 60, range: 0–100). One third of all UCAREs (n = 33; 34.4%) reported a decrease in patient numbers by more than 75%. Only 5% of UCAREs reported that their patient numbers did not change (n = 5; 5.4%; Figure 1a).

Reduced patient referrals (n = 57; 61.3%) and urticaria clinic hours (n = 47; 50.6%) were the major reasons for the decrease in CU patient consultations due to the COVID-19 pandemic (Figure 1b). Almost half of the responding UCARE physicians were involved in COVID-19 patient care, in inpatient clinics (n = 23; 25.7%), outpatient clinics (16; 17.9%), or intensive care units (n = 3;3.3%) (Table 2). One in four of the affected physicians (*n* = 14, 23%) agreed or strongly agreed that these reassignments negatively impacted on the care of urticaria patients at their UCARE.

3.2 | The COVID-19 pandemic affects the way UCAREs interact with their patients

Face-to-face consultations decreased significantly during the pandemic, from 90.2% to 34.2% ($p < 0.0005$). Instead, more consultations were done via phone calls (35.8%, up from 4.7%; $p < 0.0005$), WhatsApp (11.5%, up from 3.0%; $p < 0.0005$); email (7.2%, up from 2.5%; $p < 0.0005$), and video calls(2.5%, up from 0%; $p < 0.007$) (Figure 2).

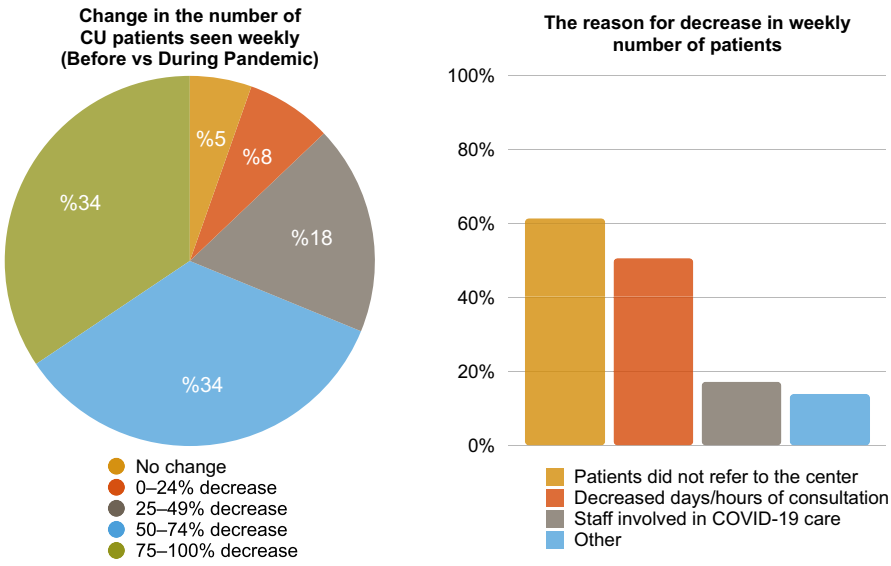

FIGURE 1 (A and B) The changes in the number of CU patients seen weekly during the pandemic and the reason for decrease in number of patients

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TABLE 2 The involvement of UCARE personnel in the care of patients with COVID-19 during the pandemic

	Responding UCARE physician	Other physicians at the UCARE	Other UCARE personnel[a]
Not involved, % (n)	61.8 (55)	44.8 (39)	51.8 (43)
Yes, in outpatient clinics, % (n)	17.9 (16)	30.8 (26)	20.4 (17)
Yes, in inpatient clinics, % (n)	25.7 (23)	43.6 (38)	36.1 (30)
Yes, in intensive care unit, % (n)	3.3 (3)	9.2 (8)	13.2 (11)

[a]For example, nurse and technician

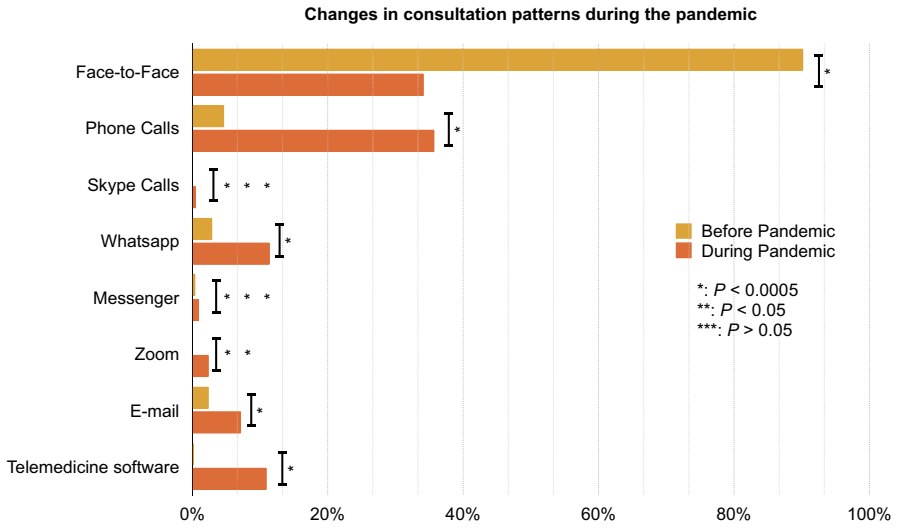

FIGURE 2 The changes in CU consultation patterns during the pandemic

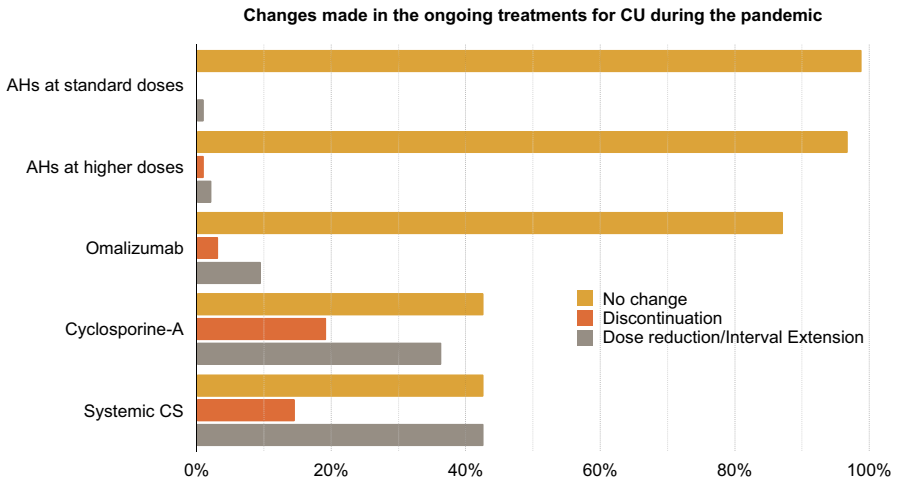

FIGURE 3 General approach to ongoing treatments for CU during the pandemic

The use of patient-reported outcome measures decreased markedly during the COVID-19 pandemic, for the Urticaria Activity Score /Angioedema Activity Score from 65.6% to 47.3%, the Urticaria/ Angioedema Control Test from 62.6% to 42.7%, the Dermatology Life Quality Index from 33.0% to 15.1%, the Chronic Urticaria Quality-of-Life Questionnaire from 30.2% to 10.8%, and for the Angioedema Urticaria Quality-of-Life questionnaire from 17.9% to 8.9% (all $p < 0.0005$).

3.3 | Cyclosporine and systemic corticosteroids, but not antihistamines or omalizumab, are used less during the pandemic

Regarding ongoing treatments, the general approach of most UCAREs during the pandemic was to discontinue or reduce the dose

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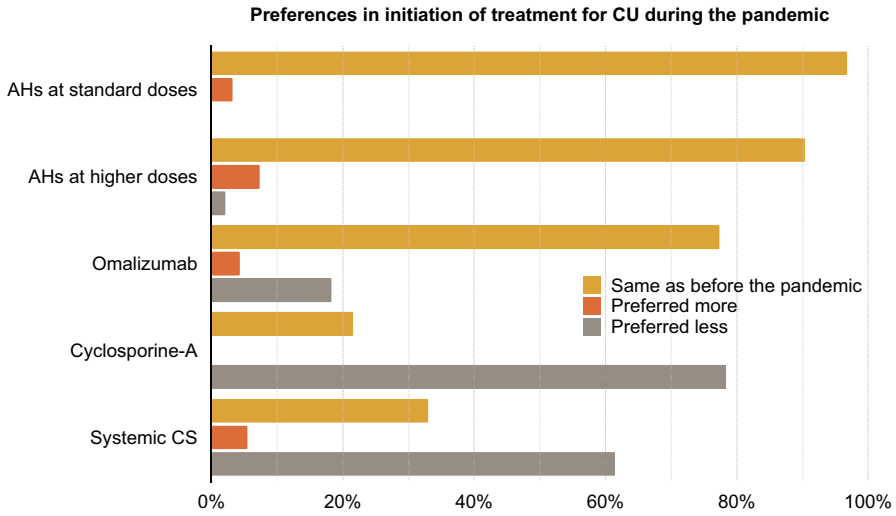

FIGURE 4 Change in the preferences in initiation of treatment for CU during the pandemic

TABLE 3 Characteristics of the CU patients diagnosed with COVID-19 (*n* = 79)

Characteristics		Mean±SD/%(n)
Mean number of CU patients diagnosed with COVID–19 per center		0.78 ± 1.65 (0–10)
Mean age		43.04 ± 12.08 (18–68)
Gender	Female	75.9 (60)
Comorbidities	None	49.4 (38)
	Hypertension	22.1 (17)
	Diabetes mellitus	7.8 (6)
	Asthma	6.5 (5)
	Hypothyroidism	5.2 (4)
Active CU treatment at the time of the diagnosis	Antihistamines at standard doses	21.5 (17)
	Antihistamines at higher than standard doses	22.8 (18)
	Omalizumab	24 (19)
	Cyclosporine A	2.5 (2)
	Omalizumab and antihistamines	10.1 (8)
	Ligelizumab	1.3 (1)
	Methotrexate	1.3 (1)
	Omalizumab, antihistamines, and systemic corticosteroids	1.3 (1)
Outcome of COVID–19	Ambulatory	86.1 (68)
	Hospitalized—mild disease	10.1 (8)
	Hospitalized—severe disease	3.8 (3)
The course of CU during COVID–19	No change	55.7 (44)
	Better	7.6 (6)
	Worse	36.7 (29)

of systemic corticosteroids (n = 51, 57.3%) and cyclosporine (n = 49, 55.7%) and to continue antihistamine (n = 92; 98.9%) and omalizumab treatment (n = 82, 87.2%; Figure 3).

All of the responding UCARE physicians agreed that antihistamines at standard or higher doses can be continued in CU patients who contract COVID-19, and almost all (92.6%) agreed that omalizumab can be continued. In contrast, only 24.2% agreed that immunosuppressive treatments can be continued.

As for the initiation of new treatments during the pandemic, most UCAREs used cyclosporine (n = 69; 78.4%) and systemic

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TABLE 4 Number of patients with a mild course of COVID-19, treated as outpatients or inpatients and number of hospitalized patients with severe COVID-19 and the treatment they received for their CU at the time they were diagnosed with COVID-19

	Severity of COVID−19		
CU treatment at time of COVID−19 diagnosis	Mild disease outpatient care	Mild disease hospitalized	Severe disease hospitalized[4]
AHs only[1]	29	6	-
Omalizumab[2]	24	1	2
Immunosuppression[3]	3	1	-
No active treatment	2	-	1
Unspecified	9	-	-
Ligelizumab	1	-	-

[1]At standard or higher doses,[2]± AHs,[3]includes cyclosporine, systemic corticosteroids, methotrexate ±AHs, and/or omalizumab.[4]The three patients who were hospitalized were 45, 54, and 65 years old. Two of them were male. The female patient was obese, the others had no comorbidities. In two of them, the CU got worse.

TABLE 5 The link of COVID-19 severity and CU exacerbation

CU Course	Non-hospitalized	Hospitalized
Better	7.3 (5)	9.1 (1)
No change	61.8 (42)	18.2 (2)
Worse	30.9 (21)	72.7 (8)
	Patients with exacerbation of CU	**No exacerbation of CU**
Hospitalized	27.6 (8)	6 (3)
Non-hospitalized	72.4 (21)	94 (47)

corticosteroids (n = 56; 61.5%) less often, but omalizumab as often as before (n = 72; 77.4%; Figure 4).

3.4 | Chronic urticaria does not appear to affect the course of COVID-19, but COVID-19 results in CU exacerbation in one of three patients

Of 79 CU patients with COVID-19 (76% female, mean age: 43.0 ± 12.1 years; 18–68), 76 (96%) showed a mild course of COVID-19, with 11% and 89% of them receiving inpatient and outpatient care, respectively. Only 3 patients had severe disease and none died (Table 3). Forty-four (55.7%) of CU patients were on antihistamines, 26 (32.9%) on omalizumab, and 2 (2.5%) on cyclosporine at the time of their COVID-19 diagnosis. No change in CU treatment was made in 70.9% of the patients following COVID-19 diagnosis (Table 4). There was no statistically significant relationship between CU treatment and COVID-19 severity (mild vs severe disease).

The course of CU did not change in 55.7% of the patients, while 36.7% were reported to experience exacerbation and 7% improved. Patients who experienced exacerbation of their CU upon contracting COVID-19 more often required hospitalization because of the course of their COVID-19, in 28% vs 6% of cases. Vice versa, the rate of CU exacerbation in hospitalized patients was higher than in non-hospitalized patients (73% vs 31%; $p < 0.05$; Table 5).

4 | DISCUSSION

This is the first study on the effects of the COVID-19 pandemic on patients with CU and their care at specialist centers. Our findings show that the pandemic severely impairs CU patient care at UCAREs, markedly changes physician-patient interactions, and affects how patients are treated. Our results also indicate that CU is not linked to severe COVID-19, but often worsened by it.

CU is a chronic condition that often comes with fluctuating disease activity and with severe disease and insufficient treatment response to antihistamines in most patients. Access to specialized urticaria centers such as UCAREs is therefore crucial, and our data illustrate that this access is severely restricted by the pandemic, with less than half of patients seen at UCAREs than before the pandemic. The short- and long-term consequences of this remain to be seen but must be expected to include deterioration of disease control, increased impairment of quality of life, loss of productivity, and higher rates of frustration, depression, and anxiety in affected patients. Decreased patient referrals are a main reason for the decline in patient consultations. This suggests that referring physicians, but also patients, should be informed that it is important to continue to seek the help of UCAREs. Referring physicians and patients should be made aware of remote consultation services that UCAREs offer and be encouraged to use them.

How does the COVID-19 pandemic affect the way UCAREs interact with their patients? During the pandemic, preventive measures

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have been implemented worldwide to adjust outpatient healthcare services and decrease direct patient contacts to a minimum, in line with current recommendations.[10] Our study shows that UCAREs are very much on board with this strategy: The rate of face-to-face consultations decreased by 62%, from 90% of consultations to less than half, whereas the rate of remote consultations, mainly done by phone calls and WhatsApp, increased by more than 600%, from one in 10 consultations to more than two thirds. Remote consultations have been shown to be a useful tool during the COVID-19 pandemic,[20,21] but the long-term consequences of remote care for patients with CU in terms of costs, benefits, impact on physician/patient relation, data protection and confidentiality, comfort, risk of malpractice, and effectiveness of disease management remain to be characterized.[22,23]

CURICT, a recent UCARE study of the use of Internet and communication technologies (ICTs) by patients with urticaria, found that almost all CU patients have access to ICTs and that most patients use ICTs regularly to obtain CU-related information.[24] As for the interaction of patients with their physicians, WhatsApp and email were the preferred ICTs, similar to patients with asthma or cancer.[25] WhatsApp is the most popular messaging service around the world and allows smartphone users to exchange texts, images, videos, and audio messages.[26] In our study, WhatsApp was the second most preferred ICT used for remote consultations by UCAREs, after phone calls. The use of WhatsApp comes at low or no costs, but there are concerns of patient data protection and confidentiality. Clearly, there is a need for the improvement of remote care of patients and the use of inexpensive, safe, and accessible tools for this.

The reduced use of patient-reported outcome measures (PROMs) during the pandemic is a major cause of concern. PROMs guide treatment decisions and help to monitor treatment outcomes. Current guidelines recommend the use of PROMs to assess disease activity, impact, and control at every CU patient visit. PROMs may be especially helpful during the current pandemic, with disease activity, impact, and loss of control expected to increase in many patients with CU. The UCARE network is currently developing means for administering and reviewing CU PROMs remotely, a timely and much needed effort.

Our study shows that the COVID-19 pandemic does not significantly affect the use of first-, second-, and third-line therapies for CU at expert centers. Ongoing treatments with antihistamines and omalizumab were maintained and dosing was not modified by most UCAREs (98.9% and 87.2%, respectively). Also, the initiation of antihistamine and omalizumab treatment has not changed at most UCAREs during the pandemic (96.8% and 77.4%, respectively). This is in line with current recommendations for urticaria and other mast cell-driven diseases.[10,11,27,28] With respect to the implementation of international guidelines during the pandemic, the first three lines of treatments, that is, a standard-dose antihistamine, an updosed antihistamine, and omalizumab, should be continued to be used as recommended. The use of immunosuppressive therapies for CU including the fourth-line treatment cyclosporine should be avoided if possible, emphasizing the need for the development of novel and non-immunosuppressive treatments for CU.

Given the possible role of mast cells in COVID-19–related lung damage and the results of a recent study of the effects of H1 and H2 antihistamines in patients with COVID-19, antihistamine treatment may have added benefit during the pandemic. Although the study was not randomized, placebo-controlled, or blinded, the combined use of H1 and H2 antihistamines led to decreased mortality compared to literature data in patients with severe to critical pulmonary COVID-19 symptoms.[29] The same may be true for omalizumab. A meta-analysis of randomized controlled trials in chronic spontaneous urticaria showed similar rates of upper respiratory tract infections in omalizumab and placebo-treated patients.[30] Also, omalizumab treatment was reported to reduce disease duration and viral shedding in rhinovirus infection in children with asthma,[31] possibly by enhancing anti-viral immunity via downregulation of the high-affinity IgE receptor on plasmacytoid dendritic cells (pDCs), which are essential for anti-viral immune responses.[32] Moreover, recent reports have demonstrated the effective and safe use of omalizumab in COVID-19 patients with urticaria, asthma, and urticarial vasculitis.[18] Based on these data, the most recent recommendations by several groups of experts are to continue omalizumab treatment in CU patients with mild-to-moderate COVID-19 course, or when SARS-CoV-2 infection is suspected, and to only consider prolongation of the injection interval or treatment interruption in CU patients with severe COVID-19 course.[11] UCAREs share this view, with 93% in agreement that omalizumab can be continued in CU patients with COVID-19.

In contrast, the majority of UCAREs (78.4% and 61.5%, respectively) reported that they use cyclosporine and systemic corticosteroids less often since the onset of the pandemic regardless of whether patients have COVID-19 or not. Ongoing treatments with these agents were discontinued or the dose was modified in more than 50% of patients. This change in CU management is supported by the increased risk of infection that comes with these therapies, both showing strong and non-selective immunosuppressive effects.[33,34] Three out of four UCAREs (76%) agree that immunosuppressive treatments should be discontinued in CU patients with COVID-19. As of now, there are very few studies on the global impact of the pandemic on other specialties and patient populations. From what has been published, other specialties and the care for patients with chronic diseases appear to be affected in similar ways and extent as compared to what we found to be the case for CU. This also relates to the changes in treatment linked to the pandemic. A recent study performed among allergists, for example, reported that one third of participating physicians stopped systemic steroid treatment in their patients with asthma.[35] Another study performed among rheumatologists found that one third of participating physicians reported that at least 10% of their patients had self-discontinued or reduced their immunosuppressive medication to mitigate the risk of COVID-19.[36]

Does chronic urticaria affect the course of COVID-19? The results of our study suggest that this is not the case, but the number of patients analyzed was low. Most COVID-19 patients show a mild (40%) or moderate (40%) course, whereas 15% develop severe disease and need oxygen support, and 5% have critical disease with

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respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury.[37] Of the 79 patients with CU and COVID-19 in our study, 96% showed a mild course of COVID-19, with 11% and 89% receiving inpatient and outpatient care, respectively. Only 4% of our CU patients had a severe course of COVID-19. The course of COVID-19 in CU patients did not seem to be affected by their urticaria treatment. More data are needed, from CU patients with COVID-19 and age- and sex-matched controls. The CU patients in our study were mostly young adults and female, features linked to mild COVID-19.

Does COVID-19 affect the course of CU? COVID-19, in more than a third of patients (36%), resulted in CU exacerbation, and exacerbation was more common in patients hospitalized for COVID-19, that is, patients with severe COVID-19. From a clinical perspective, this does not come as a surprise. There are more than 200 reports of acute urticaria associated with COVID-19, which were reviewed in a recent analysis.[38] More than half of these cases of acute urticaria (55%) presented during or preceding COVID-19 infection, disappeared or improved in most of the cases in less than one week, and responded favorably to treatment with AHs and topical and systemic corticosteroids. Viral infections, including infections with corona viruses, are known triggers of CU worsening,[39] although more data on the rates and relevance of this are needed. From a pathomechanistic perspective, mast cells, the key drivers of CU pathogenesis, can be activated by viruses through Toll-like receptors (TLR-4, TLR-7, and TLR-9), FcεR1, and complement receptors to release pro-inflammatory mediators and cytokines. Both SARS-CoV-1 and SARS-CoV-2 induce the release of IL-6, IL-1, and TNF-α by mast cells, consistent with the inflammatory profile observed following infection.[15] This mechanism may also explain the onset of acute urticaria in COVID-19 patients.

Stress may be another factor linking COVID-19 to exacerbation of CU. The COVID-19 pandemic comes with increased rates of elevated levels of psychological distress in the general population[40] and even higher rates in COVID-19 patients, linked to social isolation, the psychological impact of a novel severe and potentially fatal illness, concerns about infecting others, and stigma.[41] Stress leads to increased levels of neuropeptides such as substance P, which activates mast cells via the MRGPRX2. Stress is a well-known trigger of CU exacerbations.[42-45]

The strengths of our study include its global approach and scope, the high response rate of participating UCAREs, and the comprehensive assessment of the impact of the pandemic on CU patients and their care at specialist centers. As for limitations, our study of CU patients with COVID-19 is preliminary, since the number of patients included is low and we did not include controls; our study is a global one, but does not include results from all countries and may, therefore, not be representative of the situation and CU patient populations in countries without UCAREs. Clearly, many questions remain to be answered. We need to learn more about the rate of acute urticaria linked to COVID-19 and the rate of progression to chronicity. More information is needed on the limitations of remote CU patient care and how to overcome it. Finally, we need to better understand the interplay between COVID-19 and other viral infections and CU, its mechanisms, and strategies to protect CU patients from COVID-19–induced CU exacerbation.

Our study shows that CU does not appear to increase the risk for a severe course of COVID-19, even in patients on biological treatment. Physicians who take care of patients with CU must be aware of the fact that those patients who contract COVID-19 are likely to experience exacerbation of their CU. It is, therefore, important to help patients to achieve and maintain control of their disease during the pandemic. We recommend maintaining ongoing treatments with antihistamines and omalizumab, and to be very cautious with the use of immunosuppressives for CU.

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