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Recommendations on the use of systemic treatments for urticaria and atopic dermatitis during the COVID-19 Pandemic: Statement of Dermatoallergy Working Group of the Turkish Society of Dermatology

COVID-19 pandemisi süresince ürtiker ve atopik dermatitte sistemik tedavilerin kullanımına ilişkin öneriler: Türk Dermatoloji Derneği Dermatoallerji Çalışma Grubu Bildirisi

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To The Editor,

Since the first emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19) in Wuhan, China in late 2019, the pathogen has spread to 210 countries/territories and finally the World Health Organization (WHO) declared a pandemic in March 2020. In Turkey, the first patient with an officially confirmed diagnosis of COVID-19 was reported on 11 March 2020. Since then, the total number of patients with a confirmed diagnosis has reached to 95591 by 21st of April, 2020[1].

Accordingly with the changing practice in medicine throughout the world due to the measures taken to control the outbreak, the number of outpatient visits in dermatology has significantly decreased and the use of teledermatology where available is encouraged[2]. These unconventional clinical settings led to increased concern both in patients treated with immunomodulatory, immunosuppressive or biologic drugs and in prescribing physicians. Several reports have been published to alleviate this concern in treatment of patients with psoriasis, atopic dermatitis and pemphigus[3–5]. Considering the lack of information and growing demand on the treatment of patients with common dermatoallergic conditions, a similar attempt has been made by the members of Dermatoallergy Working Group of the Turkish Society of Dermatology. In this article, The Working Group's recommendations on the use, monitoring and administration of systemic treatments for chronic spontaneous urticaria (CSU) and atopic dermatitis (AD) based on the current evidence and expert opinions will be summarized. The recommendations have been developed and decided through an instant messaging program (Whatsapp, Facebook Inc, USA) with the participation of the members of the Working Group. Following the determination of the subheadings, a thorough literature review has been performed. A draft manuscript was prepared in the light of the available data on the literature, clinical experiences of the experts and extensive discussions. Thereafter, a consensus was reached individually for all suggestions made by the authors and the final version of the manuscript has been formed.

Although the pathogenesis of COVID-19 has not been fully understood yet, two phases of immune responses are thought to be involved. During the early phase of the infection, the acquired immune responses are directed to eradicate the virus and halt the progression of the disease. Following the damage of the lung, however, excessive secretion of inflammatory cytokines (e.g. IFN-α, TNF-α, IL-1β, IL-6) and chemokines, also known as "cytokine storm", contributes to the development of acute respiratory distress syndrome (ARDS), the principal cause of mortality in COVID-19[6,7]. An increased prevalence of thrombotic events has also been reported as a result of inflammation and endotheliitis[8]. Urticaria has also been reported among the cutaneous manifestations in 1.4% of the patients with COVID-19[9]. Risk factors for severe disease and mortality include older age (>70 years), male gender, pre-existing respiratory and cardiovascular disease (e.g. hypertension), diabetes, cancer, obesity and smoking[10]. On a recent analysis of risk factors and clinical manifestations of COVID-19, the authors concluded that allergic diseases are not among the risk factors for COVID-19[9]. Currently there is little evidence on the effect of systemic immunomodulatory, immunosuppressive or biologic drugs used in dermatology on the course of COVID-19. It might be postulated that broad suppression in multiple immune pathways caused by conventional immunosuppressives (glucocorticoids, azathioprine, cyclosporine, mycophenolate mofetil, and methotrexate) are more likely to increase the risk of infection and complications, particularly in the early stages of COVID-19 and/or in patients with aforementioned risk factors, rather than the biologics causing targeted immunosuppression[11]. Accordingly, the randomized controlled trials investigating the effects of omalizumab and dupilumab on CSU and AD did not show an increased risk of infection compared to placebo[12,13]"ISSN":"10976825","abstract":"Background Chronic spontaneous urticaria (CSU. On the other hand, recent series from Italy did not show an increased risk for complications of SARS-CoV-2 in patients with chronic arthritis (treated with anti-TNF , JAK inhibitors and low-dose methotrexate) or liver transplant compared to general population[14,15]with more than 33 000 confirmed patients and 1250 requiring admission to the intensive care unit within 1 month. Since the first reports of COVID-19 cases in Italy, we have circulated a survey with a 2-week follow-up contact to patients with chronic arthritis treated with biological disease-modifying antirheumatic drugs (bDMARDs. An important point is that, it is difficult to predict whether the abrupt cessation of immunosuppressive/immunomodulatory drugs and biologics would exacerbate the cytokine storm or not. For instance, IL-4, the target of dupilumab, was reported to inhibit SARS-CoV replication as a result of ACE2 downregulation[16]. However, recently, dupilumab was proposed as an agent that could be beneficial in severe ARDS by alleviating cytokine storm[17]. A recent report from Italy described two patients with AD who continued dupilumab treatment during COVID-19 and successfully recovered from the infection[18]. Another group from Italy recommended continuing dupilumab during COVID-19 pandemic based on the observations of elevation of Th2 cytokines in COVID-19 and fatal cases of SARS-CoV and the effect of IL-6 on polarizing Th1/Th2 balance to the Th2 direction[19].

In general, commencement of treatment with systemic immunosuppressants including biologics should be delayed based on a tailored risk/benefit analysis. However, this may not be possible in patients with severe disease activity. Ongoing treatment of urticaria and AD with immunosuppressive drugs and biologics may be continued unless there is active infection or high-risk exposure to SARS-CoV-2. Abrupt discontinuation of these drugs should be avoided as it may result in worsening of the disease, which may also increase the tendency to infections in patients with AD. Immunosuppressive drugs should be temporarily discontinued following the exposure to SARS-CoV-2 until obtaining a negative test result for COVID-19 or two weeks of symptom-free period. In case of symptoms strongly suggesting COVID-19 or confirmed diagnosis of COVID-19, immunosuppressants should be stopped. Currently, there is no evidence to make definitive statements for patients treated with omalizumab and dupilumab, although the

existing literature data regarding infectious adverse effects indicates a low-risk for these two agents. The Working Group's general statements for patients and recommendations for each treatment in different scenarios are summarized in Tables 1-3. The authors recommend to make decisions based on mutual agreement and to obtain an informed consent for each decision.

Considering the sparse literature data on the effects of these drugs on COVID-19, the recommendations should be interpreted with caution. We recommend social isolation, hand hygiene measures along with a tailored and shared decision making for each specific situation based on evidence instead of fearmongering by speculations and rumours that may hamper the treatment of patients and increase the "collateral damage" of the outbreak and hope that this document will comprise a basis for this approach.

Table 1. General recommendations for patients with chronic urticaria and atopic dermatitis

Patients and doctors should decide on how to reduce healthcare encounters and potential exposure to COVID-19 (e.g.; remote health care such as teledermatology, increased dosing intervals between medications)[20]
Strategies for coping with stress to prevent disease exacerbation
Patients should be informed on general preventive measures like social distancing and hand hygiene and skin care to prevent exacerbation or development of hand eczema
The regular home use of urticaria activity score and urticaria control test should be encouraged, the scores may be evaluated remotely by the physician (e.g. by e-mail). (Patients with chronic spontaneous urticaria)

Table 2. Systemic immunomodulatory/immunosuppressive drugs used for the treatment of chronic spontaneous urticaria and atopic dermatitis

Drug name	Drug class	Mechanism of immune action	Possible Risk
Systemic glucocorticoids	Steroids	Suppression nuclear factor-κB (NF-κB), decrease of transcription of pro-inflammatory genes. Affection of both adaptive and innate immunity	Increased risk of viral, bacterial, fungal infection, particularly at doses ≥20 mg/day of prednisolon or equivalent for ≥2 weeks[21] The CDC recommends against the use of systemic steroids during the initial phase of COVID-19 due to risk of prolonged duration of viral shedding[22,23]
Cyclosporine	Calcineurin inhibitor	Lowering the activity of T helper cells	Risk for urinary tract infection CSA>OMA[24]showing a 25.4 point improvement during treatment (P < 0.0001 Higher rates of infection in higher doses (4-5 mg/kg/day)[25] Less risk of infection compared to AZT/MMF/CS (for patients with AD)[26]
Azathioprine	Antimetabolite (purine analogue)	Blockade of purine synthesis and DNA replication	Increased risk for bacterial infections. AZT/MMF/CS>MTX/CSA (for patients with AD)[26]
Mycophenolate mofetil	Antimetabolite	Inhibition of inosine monophosphate dehydrogenase and nucleotide synthesis	Increased risk for bacterial infections. AZT/MMF/CS>MTX/CSA (for patients with AD)[26]
Methotrexate	Antimetabolite (antifolate)	Inhibition of dihydrofolate reductase and macrophage activation	Less risk of infection compared to AZT/MMF/CS (for patients with AD)[26]
Dupilumab	Monoclonal antibody	IL-4Rα antagonist Blockade of IL-4 and IL-13, decrease of Th-2 induced inflammation	Upper respiratory tract infections (in general) DUP≤Placebo(6.6% vs 6.4%) Viral upper respiratory tract infections, influenza DUP<Placebo[13]including skin infections and systemic infections. Immunomodulators (e.g., anti-tumor necrosis factors, anti-interleukin [anti-IL]-23, anti-IL-17, Janus kinase inhibitors Nasopharyngitis: DUP>Placebo (15.7% vs 13.9%) (not significant) Urinary tract infections: DUP<Placebo (2% vs 2.3%) (not significant)[27] No increased risk of serious bacterial/opportunistic infections[26]
Omalizumab	Monoclonal antibody	Binding to free serum IgE and down-regulation of FcεRI	Meta-analysis of RCTs showed similar rates of upper respiratory tract infection and nasopharyngitis in patients treated with OMA or placebo[28] Decreased disease duration and viral shedding in rhinovirus infection in children with allergic asthma[29]but it is unclear whether this association is causal. Objectives: To test whether omalizumab treatment to reduce IgE would shorten the frequency and duration of rhinovirus (RV

CDC: Centers for Disease Control and Prevention; COVID-19: Coronavirus disease 2019; CSA: Cyclosporine; OMA: Omalizumab; AZT: Azathioprine; MMF: Mycophenolate mofetil; CS: Corticosteroid; AD: Atopic dermatitis; MTX: Methotrexate; DUP: Dupilumab; RCT: Randomized controlled trials

Table 3. Recommendations on the use of systemic treatments for chronic sponraneous urticaria and atopic dermatitis

	Systemic Glucocorticoids	Azathioprine/ Cyclosporine / Mycophenolate mofetil / Methotrexate/	Omalizumab	Dupilumab	H1 antihistamines
Half-life[30–32]	2-4 hours (prednisolone) 18-26 hours (methylprednisolone)	Azathioprine: 5 hours Cyclosporine: 8.4 hours (5-18) Mycophenolate mofetil:16-18 hours Methotrexate: 3-10 hours	26 days	4.8-7 days (in rats) 11.7-20.5 days (in monkeys)	
Initiation of Treatment	- Should be delayed based on a benefit/risk ratio - If clinical severity warrants a systemic treatment targeted biologics (dupilumab, omalizumab) should be preferred to immunosuppressants - If systemic corticosteroid will be used, the lowest dose and shortest duration (≤20 mg/day of prednisolone or equivalent for ≤2 weeks) should be planned.				Nonsedative H1 antihistamines should be preferred due to their favorable safety profile[33]Development and Evaluation (GRADE (ie; less dryness on the mucosa)[34] Can be used, up to 4-fold of approved doses until the disease control is obtained. - Dosing can be adjusted by the patient depending on the symptom severity (UAS, UCT)
Ongoing treatment (no infection or high risk exposure)	- May be continued unless there is active infection or high risk exposure to COVID-19. - Strict social isolation measures should be taken. - Consider extending intervals for laboratory monitoring. - Abrupt discontinuation should be avoided due to risk of exacerbation - In patients with stable disease or in remission, a gradual decrease of immunosuppressant dose should be considered. In case of disease exacerbation, the treatment may be recommenced. - In patients currently under treatment, the dosing intervals of omalizumab and dupilumab may be extended in patients with stable disease in order to decrease visits to healthcare units(e.g. The dose intervals might be extended up to 8 weeks for omalizumab,temporary discontinuation might be considered in patients with stable disease with 8-week-intervals)[35] - For omalizumab, the first three injections should be given in the hospital due to small risk of anaphylaxis. Subsequent injections might be performed in small healthcare units or at home, if licenced for home self-administration[36] - For dupilumab, home self-administration is recommended - The use of artificial tear eye drops is recommended to prevent keratoconjunctivitis sicca during treatment with dupilumab.				
Ongoing treatment (exposure to SARS-CoV-2 but no symptoms)	- Should be discontinued temporarily, until obtaining a negative test result for COVID-19 or after two weeks of symptom-free period - Glucocorticoids should not be stopped abruptly, tapering off is recommended		- Possibly lower risk compared to immunosuppressants - Tailored decision making based on patients' risk factors is recommended.		
Ongoing treatment (confirmed diagnosis or strong suspicion of COVID-19)	- Should be stopped, regardless of COVID-19 severity - Glucocorticoids should not be stopped abruptly, tapering is recommended		- Despite the low level of evidence indicating a risk, treatment might be stopped. However, recent reports indicate a beneficial effect of dupilumab on cytokine balance in COVID-19[18,19].		

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; UAS: urticaria activity score; UCT: urticaria control test

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