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 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 95,591 by 21st of April, 2020. 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. 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. Considering the lack of information and growing demand on the treatment of patients with common dermatologic 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

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 medications20. |
| 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-kB (NF-kB), 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 weeks21. The CDC recommends against the use of systemic steroids during the initial phase of COVID-19 due to risk of prolonged duration of viral shedding22,23. |
| Cyclosporine | Calcineurin inhibitor | Lowering the activity of T-helper cells | Risk for urinary tract infection CSA>OMA24 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-4Rx 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 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 placebo28. Decreased disease duration and viral shedding in rhinovirus infection in children with allergic asthma29. |

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, IL: Interleukin
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-19.6,19.

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

Table 3. Recommendations on the use of systemic treatments for chronic spontaneous urticaria and atop dermatitis

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|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| **Systemic glucocorticoids** | **Azathioprine/cyclosporine/mycophenolate mofetil/methotrexate** | **Omalizumab** | **Dupilumab** | **H1 antihistamines** |
| **Half-life** | Azathioprine: 5 hours | Cyclosporine: 8.4 hours (5-18) | Mycophenolate mofetil: 16-18 hours | Methotrexate: 3-10 hours |
| 2.4 hours (prednisolone) | Cyclometabolism: 2-4 hours (prednisolone) | 26 days | 4.8-7 days | (in rats) 11.7-20.5 days (in monkeys) |
| 18-26 hours (methylprednisolone) | | | |

**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.

**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).
- 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.
- 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.
of the patients with COVID-19. 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. 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.

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. 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. 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-α, JAK inhibitors and low-dose methotrexate) or liver transplant compared to general population. 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. However, recently, dupilumab was proposed as an agent that could be beneficial in severe ARDS by alleviating cytokine storm. A recent report from Italy described two patients as an agent that could be beneficial in severe ARDS by alleviating cytokine storm. A recent report from Italy described two patients with 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.

**Ethics**

**Informed Consent:** The authors recommend to make decisions based on mutual agreement and to obtain an informed consent for each decision.

**Peer-review:** Externally and internally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: A.S., S.A., N.A., E.B.B., M.B., F.C., T.E., Y.E., Concept: Ü.G., S.P.K., R.K., Design: G., S.P.K., R.K., Data Collection or Processing: Ö.S.K., Z.Ö., E.Ö., H.S., Analysis or Interpretation: E.Ş., O.T., S.U., E.K., Literature Search: E.Ş., O.T., S.U., E.K., Writing: A.S., S.A., N.A., E.B.B., M.B., F.C., T.E., Y.E., Ü.G., S.P.K., R.K., Ö.S.K., Z.Ö., E.Ö., H.S., E.Ş., O.T., S.U., E.K.

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**References**

1. T.C Sağlık Bakanlığı Korona Tablosu [Web Document]. URL https://covid19.saglik.gov.tr/ [accessed on 22 April 2020].
2. Villani A, Scalvenzi M, Fabbrocini G: Teledermatology: a useful tool to fight COVID-19. J Dermatolog Treat 2020;13:1.
3. Lebwohl M, Rivera-Oyola R, Murrell DF: Should biologics for psoriasis be interrupted in the era of COVID-19? J Am Acad Dermatol 2020;82:1217-8.
4. Wollenberg A, Flohr C, Simon D, et al: European Task Force on Atopic Dermatitis: A Comprehensive Pooled Analysis. Am J Clin Dermatol 2016;137:1742-50.e4.
5. Shakshuki H, Daneshparzoo M, Murrell DF, Lehman JS: Treatment considerations for patients with pemphigus during the COVID-19 pandemic. J Am Acad Dermatol 2020.
6. Li X, Geng M, Peng Y, Meng L, Lu S: Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020;10:102-8.
7. Shi Y, Wang Y, Shao C, et al: COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;27:1451-4.
8. Bickel B, Madhavan MV, Jimenez D, et al: COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. J Am Coll Cardiol 2020.
9. Zhang J, Dong X, Cao Y, et al: Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020.
10. Jordan RE, Adab P, Cheng KK: Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198.
11. Price KN, Frew JW, Hsiao JL, Shl VY: COVID-19 and Immunomodulator/Immunosuppressant Use in Dermatology. J Am Acad Dermatol 2020;82:e173-e5.
12. Zhao Z, Ji CM, Yu WJ, et al: Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2016;137:1742-50.e4.
13. Eichenfield LF, Bieber T, Beck LA, et al: Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. Am J Clin Dermatol 2019;20:443-56.
14. Monti S, Balduzzi S, Delvino P, Belli E, Quadrelli VS, Montecucco C: Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020;79:667-8.

15. D’Antiga L: Coronavirus and immunosuppressed patients. The facts during the third epidemic. Liver Transplant 2020.

16. de Lang A, Osterhaus ADM, Haagmans BL: Interferon-γ and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells. Virology 2006;353:474-81.

17. Storm C, Hawill B, Geraci J: Repurposing Dupilumab May Treat Advanced COVID-19 Patients With Severe Acute Respiratory Syndrome By Mitigating. (Preprint) (https://www.researchgate.net/publication/340084903_Repurposing_Dupilumab_May_Treat_Advanced_COVID-19_Pa_tients_With_Severe_Acute_Respiratory_Syndrome_By_Mitigating_Cytokine_Storm) [accessed on 23 April 2020].

18. Ferrucci S, Romagnuolo M, Angleri L, Berti E, Tavecchio S: Safety of dupilumab in severe atopic dermatitis and infection of Covid-19: two case reports. J Eur Acad Dermatol Venereol 2020.

19. Patruno C, Stingeni L, Fabbrocini G, Hansel K, Napolitano M: Dupilumab and COVID-19: what should we expect? Dermatol Ther 2020.

20. Pathoulas JT, Stoff BK, Lee KC, Farah R: Ethical outpatient dermatology care during the coronavirus (COVID-19) pandemic. J Am Acad Dermatol 2020;82:1272-3.

21. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG: Prevention and management of glucocorticoid-induced side effects: A comprehensive review. Infectious complications and vaccination recommendations. J Am Acad Dermatol 2017;76:191-8.

22. Russell CD, Millar JE, Baillie JK: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.

23. Management of Patients with Confirmed 2019-nCoV | CDC [Web Document]. URL https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html [accessed on 19 April 2020].

24. Savic S, Marsland A, McKay D, et al: Retrospective case note review of chronic spontaneous urticaria outcomes and adverse effects in patients treated with omalizumab or ciclosporin in UK secondary care. Allergy, Asthma Clin Immunol 2015;11:21.

25. Kultihan K, Chaveekulrat P, Komoltri C, et al: Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. J Allergy Clin Immunol Pract 2018;6:586-99.