Use of biologics in the era of COVID-19: Where do we stand?

To the Editor: The novel coronavirus disease 2019 (COVID-19) has been spreading for more than 5 months since the World Health Organization declared the COVID-19 pandemic in March 2020. As of August 26, the pandemic had resulted in 23 million confirmed cases and 810,000 deaths worldwide. As the likelihood of prolonged spread without sudden termination of this situation increases, the topic of infection risk in patients treated with biologics is becoming crucial in the dermatologic field. Therefore, we conducted a PubMed search for articles reporting biologics exposure and reviewed guidelines on biologics use published during this pandemic.

Although according to phase 2 and 3 clinical trials the most frequently experienced adverse effects of biologics include upper respiratory tract infection, nasopharyngitis, or both, no significant increase in the risk of infection has been observed in treated groups compared with control groups. However, in most clinical studies, data on the incidence of lower respiratory tract infection (main pathogenicity of COVID-19) for each drug are insufficient, probably because of lack of investigator interest and low incidence (less than 5%).

The risk of COVID-19 infection in dermatologic patients treated with biologics can be assessed, focusing on areas in which COVID-19 has spread rapidly (Table I). Although the control for biologics-treated groups is the general population rather than patients treated without biologics, the proportion of polymerase chain reaction–confirmed cases in the biologics-treated group is low (approximately 0%-1.8%). Given that the proportion of suspected (not confirmed but symptomatic) cases in the biologics-treated group varies by study, with up to 18% suspected cases being reported, it is important to distinguish and manage high-risk patients. To properly interpret these data, it is necessary to face the limitations of remarkably low proportions of infected patients in the biologics-treated group, limited adjustment of clinical parameters, and heterogeneity of design between studies.

Although conventional guidelines prohibit the use of biologics for acute severe infection, the need for recommendation with detailed risk stratification has been raised in preparation for various conditions that fit the current situation. Several expert opinions or consensus statements have been reported recently (Table II). It is generally recommended that asymptomatic low-risk patients continue treatment based on dosing schedule interruption, dysregulated immunogenicity (eg, antidrug antibody), and proven safety, whereas infected patients should discontinue treatment. Furthermore, dermatologists should make sound judgments depending on the circumstances (withholding, down-dosing, or postponement) for patients with exposure history or those at high risk. However, the definitions of high-risk factors vary, and information on restarting treatment for patients who have terminated treatment or initiating treatment for biologics-naive patients is limited.

In conclusion, with advances in the understanding of COVID-19 pathogenesis and opposing suggestions of certain biologics as an alternative treatment option for COVID-19 disease, it will be necessary for guidelines about biologics use to be consistently modified and integrated at the pannational level in the COVID-19 era. Moreover, the guidelines need to be tailored to each condition, considering the differences in the prevalence of COVID-19, the incidence of pulmonary complications, quarantine policy, and insurance coverage of biologics between countries.

Young Bin Lee, MD, and Seung Phil Hong, MD, PhD

From the Department of Dermatology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea.

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Correspondence to: Seung Phil Hong, MD, PhD, Department of Dermatology, Yonsei University Wonju College of Medicine, Ilsan-ro 20, Wonju, Gangwon, 26426, Republic of Korea

E-mail: hongsp@yonsei.ac.kr
Table I. Cohort studies for incidence of coronavirus disease 2019 infection in patients treated with biologics for dermatologic disease (listed in sample number)

| Author         | Country | Patients        | Count | Age, years | Sex ratio (M:F) | Type of biologics (%) | No. of COVID-19–infected patients (%) | Control group (general population) |
|----------------|---------|-----------------|-------|------------|-----------------|-----------------------|----------------------------------------|-----------------------------------|
| Gisondi P et al<sup>1</sup> | Italy   | Psoriasis       | 5206  | 53.2 ± 11.2| 1:0.84          | Anti–TNF-α antibody (32.2) Anti–IL-12/23 antibody (26.7) Anti–IL-23 antibody (2.7) Anti–IL-17 antibody (38.3) | 6 (0.12)                              |                                    |
| Damiani G et al<sup>2</sup> | Italy   | Psoriasis       | 1193  | 55         | 1:0.47          | Anti–TNF-α antibody (19.9) Anti–IL-12/23 antibody (45.4) Anti–IL-17 antibody (5.2) | 22 (1.84)                            | 10,060,574 54,801 (0.54)         |
| Gisondi P et al<sup>3</sup> | Italy   | Psoriasis       | 980   | 56.4 ± 12.4| 1:0.72          | Anti–TNF-α antibody (50.0) Anti–IL-12/23 antibody (17.0) Anti–IL-23 antibody (0.0) Anti–IL-17 antibody (28.0) | 0     | 257,353 3199 (1.24) |
| Carugno A et al<sup>4</sup> | Italy   | Psoriasis       | 159   | 51.5 ± 14.0| 1:0.39          | Anti–TNF-α antibody (33.3) Anti–IL-12/23 antibody or anti–IL-23 antibody (18.9) Anti–IL-17 antibody (47.8) | 29 (18.24)<sup>*</sup>              |                                    |
| Giulia R et al<sup>5</sup> | Italy   | Hidradenitis suppurativa | 96   | 35 | ND | Anti–TNF-α antibody (47.9) Anti–IL-17 antibody (11.5) | 0 |                                    |
| Carungo A et al<sup>6</sup> | Italy   | Atopic dermatitis | 30   | 35.5 ± 11.9| 1:0.5           | Anti–IL-4/13 antibody (100.0) | 0 |                                    |

COVID-19, Coronavirus disease 2019; F, female patients; IL, interleukin; M, male patients; ND, not described; TNF, tumor necrosis factor.

*Estimated for patients with suspected COVID-19 (not polymerase chain reaction confirmed).

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Table II. Expert opinion* or official statement for recommendation of biologics use in dermatologic patients

| Author/organization | Subjects for recommendation | Current risk of patients for COVID-19 infection | Recommendation for current treatment | Initiation for biologic-naive patients | Remarks |
|---------------------|-----------------------------|-----------------------------------------------|-------------------------------------|----------------------------------------|---------|
| International Psoriasis Council<sup>1</sup> | Treated for psoriasis with any biologics | COVID-19 infected | Discontinuation | High risk, no CSS | Depends on situation | High risk: >60 y, comorbidities (CVD, DM, hepatitis B, COPD, CKD, cancer) |
| Price KN et al<sup>2</sup> | Treated with anti-TNF-α antibody | No CSS or mild CSS | Continuation | Continuation | Discontinuation or dose reduction | |
| Treated with anti-IL-4/13 antibody | CSS worsening or high fever | Continuation | Discontinuation or dose reduction | |
| Treated with anti-IL-17, anti-IL-12/23, and anti-IL-23 antibody | Severe CSS | Continuation | Discontinuation or dose reduction | |
| American Academy of Dermatology<sup>3</sup> | Treated with any biologics | No CSS | Continuation | Postponement or change to alternative agent | High risk: >60 y, comorbidities (CVD, DM, severe HTN, liver disease, kidney disease, pulmonary disease, cancer), current smoker |
| Treated with any biologics | High risk, no CSS | Continuation | Discontinuation or dose reduction | |
| Australian Medical Dermatology Group<sup>4</sup> | Treated with any biologics | No CSS | Continuation | Depends on situation | High risk: >60 y, uncontrolled or multiple comorbidities (CVD, CKD, DM, HTN, cancer), high dose or multiple use of other immunosuppressive agent, history of severe/recurrent respiratory tract infection |
| Treated with any biologics | High risk, no CSS | Continuation | Discontinuation or dose reduction | |
| COVID-19 infected | Discontinuation or dose reduction | |
| | COVID-19 infected | Discontinuation or dose reduction | |
| | | Discontinuation or postponement (if next injection is scheduled within 31 d) | |

Continued
| Author/organization | Subjects for recommendation | Current risk of patients for COVID-19 infection | Recommendation for current treatment | Initiation for biologic-naive patients | Remarks |
|---------------------|----------------------------|-----------------------------------------------|-------------------------------------|---------------------------------------|---------|
| Brownstone ND et al  | Treated for psoriasis with any biologics | High risk, no CSS | Discontinuation or dose reduction | | High risk: elderly, CVD, HTN, lung disease, DM, cancer, concomitant use of other immunosuppressive agent, immunosuppressive state (HIV), history of infection during biologics treatment |
|                       |                            | Exposure to COVID-19—infected patient | | Discontinuation or dose reduction | |
|                       |                            | COVID-19 infected | Holding a dose | | |
| Amerio P et al 6       | Treated with any biologics | No CSS | Continuation | | |
|                       |                            | High risk and CSS | Discontinuation | | |
|                       |                            | High risk and exposure to COVID-19—infected patient | Discontinuation | | |
| Reynolds SD et al 7    | All biologics-treated children | No CSS | Continuation | | For dupilumab, 50% of experts agree to continue |
|                       |                            | CSS | Depends on situation | | For dupilumab, 50% of experts agree to continue |
|                       |                            | High risk and exposure to COVID-19—infected patient | Discontinuation or depends on situation | | For dupilumab, 16% of experts agree to continue |
|                       |                            | COVID-19 infected | Discontinuation | | |
| Conforti C et al 8     | All biologics treated | COVID-19 infected | Discontinuation | | |
| Patruno C et al 9      | Anti—IL-4/13 antibody treated | No CSS | Continuation | | Change to self-injectable agent/home infusion (if possible) |
| Sanchez DP et al 10    | All biologics treated | CSS | Holding a dose | | Enhancement of self-isolation for patients treated with secukinumab and adalimumab |
|                       |                            | No CSS | Continuation | | |
|                       |                            | COVID-19 infected | Discontinuation | | |
| Galimberti F et al 11  | All biologics treated | No CSS | Continuation | Postponement | | |
|                          | COVID-19 infected | Discontinuation | Change to alternative agent | Postponement |
|--------------------------|-------------------|-----------------|-----------------------------|--------------|
| Anti–TNF-α antibody treated | COVID-19 infected | Discontinuation | Change to alternative agent | Postponement |
| Anti–IL-17 antibody treated | No CSS            | Continuation    |                             |              |
| Anti–IL-12/23 antibody treated | COVID-19 infected | Discontinuation |                             |              |
| Anti–IL-23 antibody treated | No CSS            | Continuation    |                             |              |
| Anti–IL-4/13 antibody treated | COVID-19 infected | Discontinuation | Possible                    |              |
| Anti–IL-12/23 and Anti–IL-23 antibody treated | No CSS            | Continuation    | Possible                    |              |
| All biologics for psoriasis and atopic dermatitis treated | No CSS            | Continuation    |                             |              |

**Notes:**
- CSS: COVID-19 suspected symptom
- CVD: cardiovascular disease
- DM: diabetes mellitus
- HTN: hypertension
- IL: interleukin
- TNF: tumor necrosis factor
- CKD: Chronic kidney disease
- COPD: chronic obstructive pulmonary disease
- COVID-19, coronavirus disease 2019
- CSS: COVID-19 suspected symptom
- CVD: cardiovascular disease
- DM: diabetes mellitus
- HTN: hypertension
- IL: interleukin
- TNF: tumor necrosis factor

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