REVIEW

Consensus Guidelines in Usage of Biologics in Dermatology during COVID-19 Pandemic: Biologic Advisory Group Malaysia

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Objective

The aim of this Biologic Advisory Group (BAG) Malaysia consensus guideline is to provide clinicians managing cutaneous diseases with biologics relevant parameters to consider prior to initiating or stopping or continuing any biologic treatment in the current landscape of the COVID-19 pandemic. Besides reviewing the medical literatures on COVID-19 and evidences related to other human coronavirus or influenza, expert opinions and clinical experiences are shared and debated in formulation of this biologic consensus guideline.

Preamble

The emergence of the 2019 novel coronavirus SARS-CoV-2 in December 2019 in Wuhan, China and subsequently the pandemic outbreak of COVID-19 worldwide; is a great concern for public health around the world. There is a significant global concern on this COVID-19 pandemic due to its widespread of transmission and its effects in significant proportion of vulnerable patients.

Patients on immunomodulators, in particular biologics and small molecules for cutaneous diseases represent one of the vulnerable populations who require special consideration with regard to their treatment during this COVID-19 pandemic period.

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Currently, the Centre for Disease Control Prevention (CDC) and World Health Organization (WHO) have no specific guidelines on the use of biologics during the pandemic.

Treating patients in this COVID-19 pandemic situation, individual clinicians would need to base on their knowledge and experience to weigh the risks versus benefits to decide whether biologics should be initiated or continued in their patients. There are some who cautioned the use of biologics during COVID-19 pandemic, while others cautioned against discontinuation of biologics which can result in loss of response when reinitiated later or formation of auto-antibodies upon discontinuation of biologics.[1-4]

There are several guidance documents published recently by the American Academy of Dermatology (AAD),[5] International League of Dermatological Societies (ILDS)[6] and International Psoriasis Council[7] with regard to the use of biologics on psoriasis patients during COVID-19 pandemic offering some general guidance to clinicians on the management of psoriasis patients with biologics during this COVID-19 pandemic.

In addition, there are some data on the risk of COVID-19 infection with biologic therapy, with recent publication of 2 studies suggesting the usage of biologics in immune-mediated inflammatory diseases is not associated with worse COVID-19 outcomes or at higher risk of being infected with COVID-19 virus.[8-9] In addition, a paper from China analysed 107 psoriasis patients on IL-17 and anti-TNF-α in pandemic epicentre Wuhan has found that patients receiving biologics do not have an increased risk of contracting COVID-19 or developing complications to COVID-19.[10] Emerging data from PsoProtect registries evaluating factors associated with adverse COVID-19 outcomes in patients with psoriasis across 25 countries also found that biologic use in moderate to severe psoriasis patients was associated with lower risk of COVID-19 related hospitalization than non-biologic systemic therapies.[11]

In Malaysia, biologic therapies have also gained acceptance and is currently playing an important role in psoriasis treatment. According to Malaysian Psoriasis Registry 2007-2018 annual report, a total of 136 adult patients received biologic treatment. The biologic therapy that are most frequently used include TNF α inhibitor [Adalimumab (36%), Etanercept (11%), Infliximab (3.6%), Golimumab (0.7%), Certolizumab (0.7%)], followed by Anti IL 12/23 Ustekinumab (34%) others (2.9%).

SARS-Cov-2 Virus and COVID-19 Disease

In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology, which were supposedly epidemiologically linked to a seafood and wet animal market in Wuhan, China[12]. This unknown virus is initially being termed "2019-nCoV" and later changed to "SARS-CoV-2" (officially known as COVID-19 disease now), a beta coronavirus closely linked to SARS-CoV (2003 SARS disease) and MERS-CoV (2011 MERs disease). On 11 Mar 2020, the WHO declared Covid-19 as a global pandemic. As of 2nd Oct 2020, 34 million confirmed cases and around 1 million deaths (3%) have been reported to WHO.[13]

The initial animal reservoir for this virus is believed to be from bats, with the intermediate hosts suspected to be pangolins.[14] Human to human transmission of COVID-19, via respiratory droplets or close contact has been detected.[15] COVID-19 has a probable asymptomatic incubation period of 2-14 days during which the virus can be transmitted.16 The rapid spread of COVID-19 virus has occurred with the basic *R0* of 2.2-2.6, meaning that on average, each individual has the potential to spread the infection to 2.2 other people.[17]

Based on the hospitalized patients data, the majority of COVID-19 cases (about 80-90%) presented with asymptomatic or with mild symptoms while the remainder are severe or critical.[18,19] The most common symptoms of COVID-19 are fever, fatigue and respiratory symptoms including cough, sore throat and shortness of breath, while intestinal symptoms were occasionally reported.[15,18] Most patients developed lymphopenia and pneumonia with characteristics pulmonary ground glass opacity changes on chest CT.[15,18]

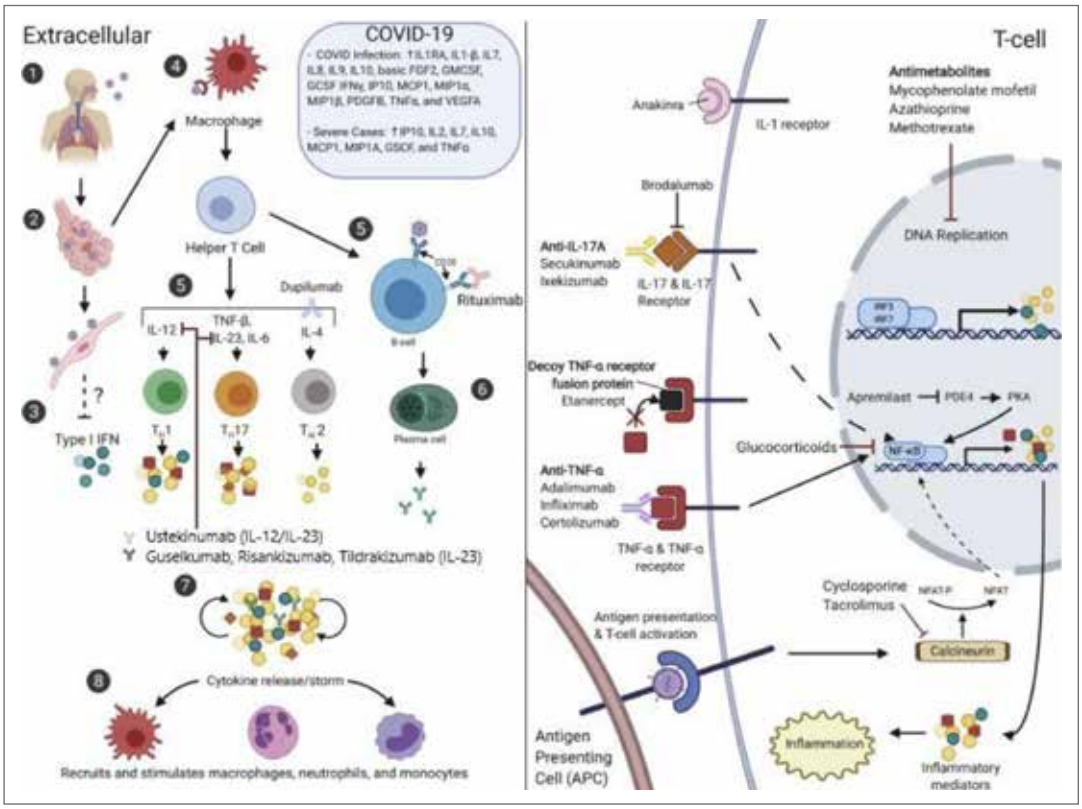
Immune Response in COVID-19 Patients

In addition, significantly high blood levels of cytokines and chemokines (inflammatory mediators) were noted in patients with COVID-19 infection. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α and TNFα that are reasoned to promote disease severity.[18] Inflammatory

mediators can become hyperactivated, resulting in a "cytokine storm" which is the primary cause of death in severe disease.[20]

Theoretical data from previous coronavirus outbreaks has also suggested a prominent role for type 1 interferon, B-cell released antibodies, tumour necrosis factor-α (TNFα) and other cytokines in the viral immune response (Figure 1).[21]

Figure 1. COVID-19 viral immune response and target of common dermatologic immunomodulators and immunosuppressants. (Adapted from Price KN et al[21])



(Left) (1) Person-to-person transmission of COVID-19 occurs through direct contact with respiratory secretions of infected individuals. The virus invades host cells by binding to their receptors and fusing with the cell membrane. (2) It is hypothesized that once inside the body, the lung epithelial cells become the primary target, where the receptor binding domain of the virus spikes bind to angiotensin-converting enzyme (ACE2) receptors of ACE2-expressing target cells. (3) Although not confirmed, it is believed the virus dampens the initial type 1 interferon (IFN) responses, which contributes to uncontrolled viral replication. (4) Once the virus is identified, macrophages present viral components to activate and induce (5) differentiation of T cells and B cells. (6) Activated B cells differentiate into plasma cells that produce antibodies important for neutralizing viruses. (7) The resulting inflammatory cytokines and antibodies continue to stimulate the production of additional cytokines and antibodies, which may contribute to the ''cytokine storm'' noted in those with severe disease. (8) The inflammatory cytokines and antibodies also promote the influx of neutrophils, monocytes, and macrophages along with additional inflammatory cytokines.

(Right) The drug targets for common dermatologic immunomodulators and immunosuppressants have also been included in this diagram. FGF, Basic fibroblast growth factor; GCSF, granulocyte-colony stimulating factor; GMCSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; IP10, interferon-induced protein 10; IRF, interferon regulatory factor; MCP1, monocyte chemoattractant protein 1; MIP1A, macrophage inflammatory protein 1-A; NFAT, nuclear factor of activated T cells; NF-B, nuclear factor-B; PDE4, phosphodiesterase 4; PDGF, platelet-derived growth factor; PKA, protein kinase A; TH, T-helper cell; TNF, tumour necrosis factor; VEGFA, vascular endothelial growth factor A.

Interleukin (IL) 1 promotes fever and the differentiation of T-helper cells to IL-17-producing T-cells. Interleukin (IL) 17 cytokines are important for immune cell recruitment to infection sites to promote clearance, while also activating downstream cascades of cytokines and chemokines. Tumour necrosis factor-α promotes dendritic cell differentiation, leukocyte recruitment, and mediates fever.[22] Antibodies produced by plasma cells help to neutralize the virus, limit infection, and prevent future infections. Disruption of B-cell differentiation into plasma cells could limit antibody production.

While normal immune response is essential to control and eliminate coronavirus infections, however, maladjusted immune responses may result

in immunopathology and impaired pulmonary gas exchange.[22]

Thus, it is currently being hypothesized that possibility of inhibiting these pro-inflammatory mediators through targeted therapy may actually improve clinical outcomes and reduce mortality in severe COVID-19 patients experiencing cytokine storm.[23,24,25,26] Two trials on tocilizumab (IL-6) in France[24] and Italy,[25] have shown clinical improvement, reduced number of ICU admissions and/or mortality in patients with severe COVID-19 pneumonia. An open label controlled trial on adalimumab (TNF-α inhibitor) for the use in treating severe COVID-19 pneumonia has also been initiated in Shanghai, China.[26]

Parameters for Consideration

In this guideline, seven (7) parameters have been considered when drafting this guideline to assess the suitability of patients to be initiated or continued with biologics during this COVID-19 pandemic. Traffic light system has been used to determine "Go" (Green); "Wait, assess other parameters" (Yellow) or "No Go" (Red) in the decision making process for this guideline. The parameters are:

1. COVID-19 Antigen (Ag) viral positivity
2. COVID-19 Antibody (IgM & IgG) seropositivity
3. Clinical signs & symptoms suggestive of COVID-19 infection or any acute respiratory infection
4. Exposure to COVID-19 positive patients
5. Underlying cutaneous disease severity
6. Patient's age
7. Underlying comorbid diseases

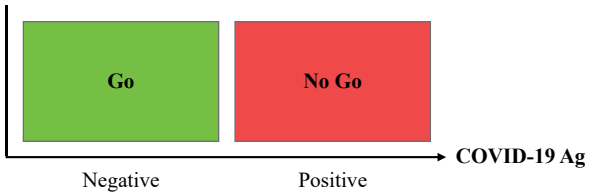
COVID-19 Antigen (Ag) Viral Positivity

This is the most important parameter to be considered in potential biologics or continuing biologics patients.

In Malaysia, there is currently no existing directive or requirement to screen all patients with COVID-19 Ag test before initiating or continuing biologics. However, for patients living in or coming from high-risk area (red zone) or suspected COVID-19 symptomatic patients, a COVID-19 Ag test is recommended.[18,19] COVID-19 RT-PCR according to the Ministry of Health should be used to establish COVID-19 infection status of the patients.

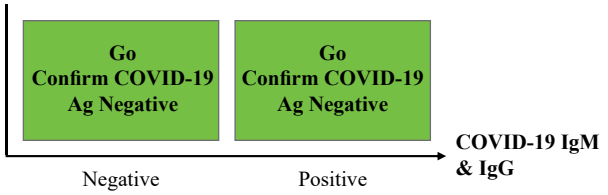
COVID-19 Ag positivity indicates current on-going infection with COVID-19 virus. Inflammatory response and mediators are needed for viral clearance.[22] Thus, it is advisable to stop patients from biologic treatment or defer initiation of biologic treatment for at least 30 days, or until patients have completely recovered and tested COVID-19 Ag negative indicating no viral shedding.[5,27]

For patients where COVID-19 Ag test is unavailable, clinicians will need to rule out COVID-19 infection in their patients through the clinical evaluation of signs & symptoms based on respective local COVID-19 practice guidelines.



COVID-19 Antibody (IgM & IgG) Seropositivity

COVID-19 Antibody test may or may not be done on the patients, as its value is limited in understanding the current infection status of the patients. Seropositivity of COVID-19 Antibody test signifies that the patient has been exposed to COVID-19 virus prior, but it does not confirm that the patient is currently still having the COVID-19 infection. Thus, we recommend those patients with either COVID-19 Antibody seropositive or seronegative to undergo COVID-19 Ag test to confirm the current status of COVID-19 infection prior to biologics initiation or continuation of therapy. If covid-19 seropositive, should WAIT and check COVID-19 Ag.



Clinical Signs & Symptoms Suggestive of COVID-19 Infection or Any Other Acute Respiratory Infection

Cold/flu-like Symptoms or Signs & Symptoms Suggestive of Any Other Acute Respiratory Infection

Patients with more severe skin disorders (e.g severe psoriasis) are inherently at increased risk of developing pneumonias of any cause.[28] While a number of clinical trials of newer biologics used in dermatology patients indicate a slight increased risk of developing upper respiratory tract infections (URTI), there does not appear to be a significant

increase risk of developing influenza (flu).

For patients with cold/flu-like symptoms, it is advisable to stop or defer biologics treatment and refer patients for COVID-19 Ag test.

For patients with cold/flu-like symptoms who are COVID-19 Ag negative, it is also advisable to screen for non-COVID-19 pathogens such as influenza, respiratory syncytial virus (RSV), Streptococcus pneumoniae so that appropriate treatment can be given. Patients with cold/flu like symptoms will still require their active immune system and inflammatory mediators for non-COVID-19 bacterial/viral clearance, thus we advised biologics treatment to be restarted after 14 days or after cold/flu-like symptoms resolves or completion of a course of antibiotics/antivirals.[29]

Diarrhoea

As the COVID-19 virus may directly or indirectly affect the enteric mucosa,[30] diarrhoea and other gastrointestinal findings should raise clinical suspicion for COVID-19 infection, with or without the presence of fever, cough and other respiratory and non-respiratory manifestation. The WHO defines diarrhoea as 3 or more loose/liquid stools per day or an increase in the number of evacuations compared with the usual.[33] A few meta-analysis conducted found that pooled prevalence among patients reporting diarrhoea ranges from 6.1% to 10.4%.[30, 31, 32]

Although the prevalence is rather low, the COVID-19 pandemic has affected millions of people worldwide, translating to a few hundred thousands of diarrhoea-associated case worldwide due to COVID-19. Thus, we recommend that patients with diarrhoea of unknown origin should have COVID-19 infection excluded before initiating or continuing biologics treatment.

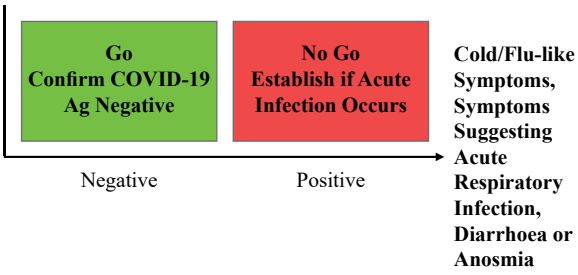
Loss of Smell (Anosmia)

There is an increasing evidence that olfactory dysfunction can present in COVID-19 patients. Anosmia can occur alone or can be accompanied by other symptoms of COVID-19, such as dry cough. However, the pathogenic mechanism of olfactory dysfunction and its clinical characteristics in patients with COVID-19 remains unclear.

There is a variability of data on anosmia among different population of patients. While it has a high incidence rate (47-70%) in COVID-19 patients in Europe[34,35] and American countries, it rarely occurs in Chinese patients (pooled data of 5%).[36]

A recent retrospective study investigating 949 patients with COVID-19 has found that 20% of the patients reported loss of smell during their initial evaluation of COVID-19. This study also found that smell loss is an independent positive prognostic factor of a less severe COVID-19 infection; significantly associated with decreased hospitalization, intensive care unit admission, intubation and acute respiratory distress syndrome rates.[37]

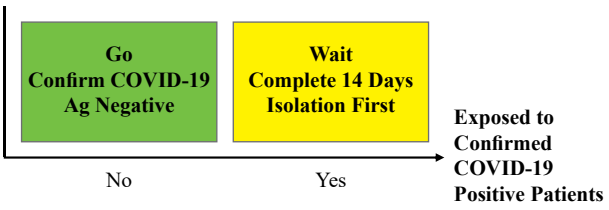
We recommend that also patients with recent onset anosmia should also have COVID-19 infection excluded before initiating or continuing biologic treatment.



Exposure to COVID-19 Positive Patients

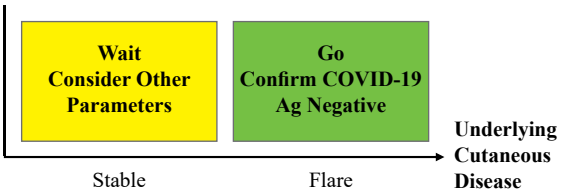
This group of patients with high risk of exposure to COVID-19 include patients living in or traveling frequently to endemic areas, healthcare worker, nursing home resident, household member or co-worker with COVID-19 infection.

These patients are of very high risk of contracting COVID-19 virus from others with close contact with them. Due to their high susceptibility in contracting the COVID-19 anytime throughout this COVID-19 pandemic, we recommend for this group of patients, a 14 days isolation or quarantine if they have been in contact with a COVID-19 positive patient. We recommend COVID-19 infection should be excluded from patients before initiation or continuation of biologics.



Underlying Cutaneous Disease Severity

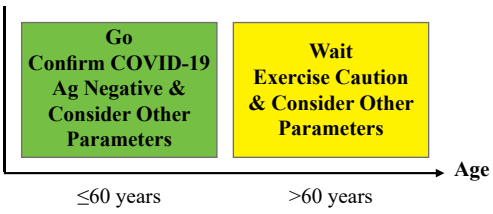
The severity of underlying cutaneous disease is also another parameter that is needed to consider when initiating or continuing biologic therapy. Disease's flare is one factor that clearly indicates benefits outweigh the risk of initiation or continuation of biologic therapy during COVID-19 pandemic. We recommend patients with a flare of underlying cutaneous disease to have the COVID-19 infection excluded before initiating or continuing biologics treatment.



Patient's Age

Patients of the older age group (>60 years old) is a known major risk factor contributing to the mortality of patients with COVID-19 disease. Death is most commonly reported among patients aged >80 years (28.7%), followed by 70-79 years (16.6%) and 60-69 years (6.7%).[19,38,39,41]

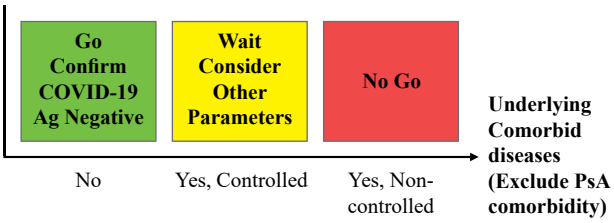
In view of this, we recommend that in patients over 60 years of age, caution need to be exercised and to take in consideration of other parameters in making a decision.



Underlying Comorbid Diseases

Data from US and China found that severe outcomes were more commonly reported for patients with reported underlying conditions (cardiovascular diseases, respiratory diseases, diabetes, liver, kidney diseases or cancer patients or on transplant patients).[24,40,41] Deaths were 12 times higher among patients with underlying conditions compared to those without reported underlying conditions.[38] As such, caution will need to be exercised considering other parameters in this group of comorbid patients.

However, for psoriasis patients with co-existing psoriatic arthritis disease, the use of biologics in these concomitant diseases are much warranted, as both diseases respond well to biologics. Thus, exception to the recommendation above for underlying comorbid disease shall be made for co-existing psoriatic arthritis disease



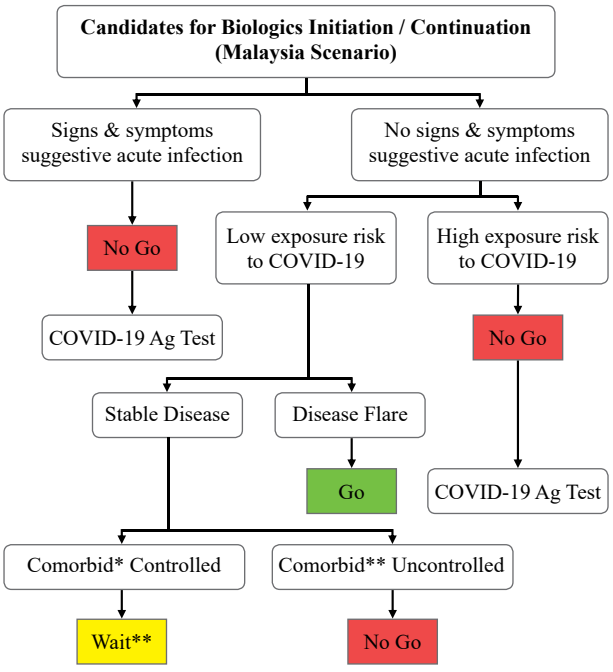
The Algorithm for The Parameters Discussed Above is Summarized in Figure 2

It is important to remember that COVID-19 is a novel, rapidly changing virus. Thus, when more data is available, this BAG Malaysia consensus guideline will need to be updated.

General Measures

Patients who have been initiated or continued with biologics treatment need to be monitored closely and advised appropriately, while those were deferred or discontinued biologics treatment will need to be monitored closely on their disease severity. In addition, all patients should be reminded to practice good infection prevention measures[10] such as frequent hand washing, wear a face mask in public places and practise social distancing.

Figure 2. Algorithm for the initiation/continuation of biologics treatment during COVID-19 Pandemic period (Malaysia Scenario)



**Including, but not limited to cardiovascular disease, respiratory disease, diabetes mellitus, liver disease, kidney disease, cancer and organ transplant patient.*

***Caution needs to be exercised, considering other parameters before initiation of biologics.*

COVID-19 Vaccination in Patients on Biologic Treatment

As of 2nd Oct 2020, there are 42 COVID-19 candidate vaccines in the clinical evaluation phase, while 151 candidate vaccines in the pre-clinical evaluation phase.[42] With vaccines companies all over the world working relentlessly to find a safe and efficacious vaccine to halt the spread of this COVID-19 infection, it is a matter of time that the right candidate vaccine will be available commercially.

COVID-19 vaccines under development include virus vaccines (inactivated or weakened), viral vector vaccines (replicating or non-replicating), nucleic acid vaccine (DNA or RNA) and protein-based vaccine (protein subunit or virus like particles).

Patients on biologic should not be given a virus vaccine. Other vaccines are not contraindicated. It is advisable for those undergoing or planning to have biologic therapy to be recommended a COVID-19 vaccination.

Key Recommendations

	BAG MY Position Statement	Level of Evidence	Strength of Recommendation
8.1	The concurrent use of biologics during the COVID-19 pandemic does not increase the risk of COVID-19 infection	II-2	B
8.2	The concurrent use of biologics during the COVID-19 pandemic does not increase the severity of COVID-19 infection	II-2	B
8.3	Patients with active COVID-19 infection as proven by positive COVID-19 Ag test or with COVID-19 clinical symptoms (without positive virology) should postpone/defer biologic treatment for a period of at least 30 days and until being tested negative at the end of the period of postponement	III	C
8.4	Patients with other active respiratory infection (other than COVID-19 infection) or with a history of close contact with a proven active COVID-19 patient should postpone/defer biologic treatment for a period of at least 14 days and until being tested negative at the end of the period of postponement	III	C
8.5	Patients with positive serology (IgM/IgG) for COVID-19 infection with negative antigen status can proceed with biologic treatment	III	C
8.6	All patients with increased risk from co-morbid diseases should be assessed on a case-by-case basis by attending physician before commencing use of biologic agents	III	C
8.7	All patients on biologics should be recommended vaccination with a COVID-19 vaccine, should it be available in the near future	III	C

Level of Evidence

Level	Study Design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferable from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic result on uncontrolled experiments (such as the results from the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case report; or reports of expert committees

Source: US/Canada Preventive Services Task Force

Strengths of Recommendation

A	At least one meta-analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

Source: Modified from the Scottish Intercollegiate Guidelines Network (SIGN)

Note: The strength of recommendations related to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Disclaimer

The recommendations stated in this guideline are based on the currently available and/or published information related to the COVID-19 and biologics usage in psoriasis disease, as well as acts as a general guide only. Individual clinicians will need to evaluate each patient based on individualized need and discuss with their patients on their diseases and consequences before initiating or continuing biologics treatment.

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Conflict of Interest Declaration

All panel members do not have direct conflict of interest.

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