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Dupilumab and COVID-19: What should we expect?

Cataldo Patruno[1] | Luca Stingeni[2] | Gabriella Fabbrocini[3] | Katharina Hansel[2] | Maddalena Napolitano[4]

[1]Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

[2]Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy

[3]Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[4]Department of Health Sciences Vincenzo Tiberio, University of Molise, Campobasso, Italy

Correspondence
Maddalena Napolitano, Department of Medicine and Health Sciences Vincenzo Tiberio, University of Molise, Campobasso, Italy.
Email: maddy.napolitano@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with high morbidity and mortality. There are very limited data on the interference of immunomodulating drugs on the risk of infection and on the course of the disease. In particular, there are no current clinical data about the interference exerted by dupilumab, a biologic drugs blocking IL-4 and IL-13, used for adult atopic dermatitis. The pathogenesis of COVID-19 is complex, characterized by an immune response mainly Th1/Th17. The hyper-activation of these cells may cause the release of pro-inflammatory cytokines that may result in lung impairment. IL-4 and IL-13 are Th2 cytokines, thus being part of a pathway not considered implicated in host defense mechanism against viral infections. Indeed, viral infections, including respiratory infections, have not been reported as a significant adverse event in clinical trials. Furthermore, dupilumab has been proved to be efficacious also in exacerbations of asthma, and it is known that viral infections can worsen asthma. Therefore, the current data seem to suggest that treatment with dupilumab should not be stopped during COVID-19 pandemic. Obviously, a careful assessment is mandatory for each individual patient and further studies are necessary to characterize the immunologic responses in COVID-19.

KEYWORDS

adult atopic dermatitis, COVID-19, dupilumab

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a potentially fatal disease that is of great world public health concern.[1] Indeed, the World Health Organization currently considers COVID-19 to be a pandemic.[2]The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to severe clinical conditions characterized by respiratory failure, sepsis, and multiple organ dysfunction syndromes.[3] The mortality rate is variable, ranging from 12% in the epicenter to 1% in the more peripheral areas of the epidemic.[4] The prognosis appears to be worse for elderly patients (mortality is about 15% in patients ≥ 80 years) and for those affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases.[3] The pathophysiology of COVID-19 has not been completely understood. Both CD4+ T and CD8+ T cells play a significant antiviral role by balancing the reaction against SARS-CoV-2 and the risk of developing overwhelming inflammation.[5] CD4+ T cells promote the production of virus specific antibodies by activating T-dependent B cells, while CD8+ T cells are cytotoxic and can kill cells infected by the virus.[5] Furthermore, the infection induces T cells to differentiate in various subsets, including T-helper1 (Th1) and Th17, and subsequent massive release of pro-inflammatory cytokines [interleukin (IL)-1, IL-6, IL-8, IL-21, TNFβ, and MCP1].[5,6] The high production of these mediators due to viral persistence (cytokine storm) is able to inhibit CD8+ T cells activation.[5,6] These important immunologic alterations may result in impaired lung functions.[5] However, SARS-CoV-2 also seems to stimulate the secretion of Th-2 cytokines such as IL-4 and IL-10 that suppress Th1/Th17 mediated inflammation.[6] Dupilumab is a fully human monoclonal

antibody that inhibits the function of IL-4 and IL-13 by blocking their shared receptor component, approved for the treatment of moderate-to-severe atopic dermatitis (AD) of the adult.[7] The question is whether this block could lead to a greater susceptibility to SARS-CoV-2 or to worsening of COVID-19. IL-4 and IL-13 are two cytokines of type-2 cell-mediated immunity, a pathway not considered crucial to host defense mechanism against most infectious agents, except some helminths.[8,9] In clinical trials with dupilumab, there was no evidence of an increase in overall infection risk rates,[8] while they were up to 11% for biologics used for psoriasis.[10] Furthermore, respiratory disorders, including viral respiratory infections, were monitored during the clinical trial program, and were not reported as adverse events.[11] Herpes virus infection incidence overall rate was slightly higher in the dupilumab groups than in the placebo group (< 1%), nonstatistically significant.[8] Notably, the incidence of eczema herpeticum and herpes zoster was higher in the placebo group than in the dupilumab groups, reflecting the well-known increased risk of herpes virus infection in patients with AD.[8] In patients affected by COVID-19, the cytokine and chemokine plasma concentration showed also an increased secretion of anti-inflammatory Th2 cytokines.[6] This type of cellular response also appears to be common to other Coronavirus-induced infections. Indeed, during SARS-CoV infection outbreak of 2002 to 2003, a significant increase in Th2 cytokines (IL-4, IL-5, IL-10) had been observed in fatal cases when compared with patients who recovered.[12] This association may suggest that is the quality of immune response to be critical, rather than magnitude.[12] Furthermore, it is known that IL-6, that plays a central role in the "cytokine storm" damaging lung in Covid-19 patients, can modulate the differentiation of CD4+ T cells into effector Th1 or Th2. Normally, the presence of IL-6 shifts the Th1/Th2 balance toward the Th2 direction using two independent approaches: (a) promoting IL-4 production and Th2 differentiation; and (b) inhibiting IFNγ production and Th1 differentiation.[13] However, the differentiation of Th2 by IL6 is dependent on endogenous production of IL-4 whose activity is significantly reduced in dupilumab patient. Furthermore, in both patients with asthma and nasal polyposis, IL-4 and IL-13 contribute to the cellular remodeling process through effects on fibrin deposition by inducing alternative activation of macrophages to the M2 type and inhibiting fibrin degradation.[14] On the other hand, it is conceivable that the blockade of the Th2 axis could induce an increased expression of the Th1/Th17 cells.[15] If on the one hand this could be partly positive, as it would give the atopic patient an opportunity to defend himself from the infection, on the other hand in case of COVID-19 it could be negative because of hyper-expression of pro-inflammatory cytokines. Furthermore, asthma is a significant comorbidity of severe AD,[16] and viral respiratory infections could induce asthma exacerbations[17]; in clinical trials, dupilumab was able to reduce severe asthma exacerbations.[18] To stopping dupilumab can also result in exacerbation of AD with a high impact on quality of life of patient and potential loss of response when treatment is reintroduced for the possible formation of neutralizing antibodies.[19] However, this occurrence is not as obvious as for biologic drugs used for psoriasis.[10,19] Moreover, due to the mechanism of action of dupilumab, drug discontinuation could be associated to higher susceptibility toward infections, even if there are no evidences supporting this hypothesis regarding SARS-CoV-2.[20] All these data seem to suggest that treatment with dupilumab should not be stopped during COVID-19 pandemic. Dupilumab also seems to have to be preferred over traditional immunosuppressive drugs (ie, cyclosporine, corticosteroids) when starting treatment in selected severe cases in pandemic period.[20] However, International League of Dermatological Society (ILDS) guidance[21] asserts that current evidence does not justify the discontinuation of dupilumab therapy for AD in healthy subjects. On the other hand, lowering of the dose of traditional immunosuppressive agents has been suggested for patients with cold/flu like symptoms but not formally diagnosed with COVID-19 disease or in selected high-risk cases.[22,23] Lowering dosage of dupilumab is associated with a dose-dependent reduction in clinical response[19] and is therefore to be considered on a very selected case-by-case basis.[22] Obviously, a careful assessment is mandatory for each individual patient reporting any side effect. Finally, further studies are necessary to characterize the immunologic responses in SARS-CoV-2 infection to elucidate the pathogenesis and the possible implications for patients affected by AD and treated with dupilumab.

CONFLICT OF INTEREST

M. N. acted as speaker for Sanofi. L. S. acted as speaker and consultant for AbbVie, Almirall, Celgene, Lilly, Novartis, and Sanofi. G. F. acted as speaker and consultant for AbbVie and Leo Pharma. K. H. acted as speaker and consultant for AbbVie and Celgene. C. P. acted as speaker and consultant for AbbVie, Novartis, Pfizer, and Sanofi.

ORCID

Gabriella Fabbrocini https://orcid.org/0000-0002-0064-1874
Maddalena Napolitano https://orcid.org/0000-0003-3309-8190

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