COVID-19 Starts the War, but Neopterin Fights the Self: Anti-Neopterin Antibodies for COVID-19 Treatment in Severe Cases

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The word "neopterin" is made up of neo, which means new, and pterin, which contains a chemical compound known as pteridine, which, in turn, is derived from the Greek word "pteros," which means wing, to denote its discovery in butterfly wings. Pteridines, which serve as pigments in butterfly wings, can act as enzyme cofactors and, in the other wing, can function as activators of the immune system (1). Neopterin, therefore, came to develop a new line of research in pteridine chemistry.

When guanosine triphosphate (GTP) cyclohydrolase I is activated, it can mediate the cleavage of purine into 7,8-dihydroneopterin triphosphate, which is intermediate to the formation of dihydrobiopterin by 6-pyruvoyl-tetrahydropterin synthase. When lacking 6-pyruvoyl-tetrahydropterin synthase, this so-called pathway of 5,6,7,8-tetrahydrobiopterin would be less active, and thus 7,8-dihydroneopterin triphosphate would be accumulated. Neopterin and 7,8-dihydroneopterin result from 7,8-dihydroneopterin triphosphate when being converted by phosphatases. Primate species and humans do, by a high chance, possess monocytes and macrophages of the highest ability to produce neopterin upon stimulation of T cells and subsequent production of by interferon-gamma (IFN-γ), which plays a crucial role in anti-microbial immunity (2). Neopterin elevation may occur in different body fluids, including serum, plasma, CSF, urine, and pleural effusion, correlated with a variety of lung-related pathologies such as malignancies and bacterial and viral infections.

Coronavirus disease 2019 (COVID-19) is an infection that primarily involves the respiratory system but does possess the capability of being extended to the nervous system. A recent study has shown that while white blood cells and IgG index are normal, neopterin increases in the cerebrospinal fluid of patients with COVID-19-associated neurological manifestations like encephalopathies, meningitis, and dysgeusia (3). Moreover, a prospective study pointed out a four-fold increased concentration of neopterin patients with COVID-19 compared to healthy people. Patients with COVID-19 fall within a spectrum of severity (4). Patients with severe COVID-19 have shown higher neopterin levels than those with a mild presentation of the disease (4).

Before the two studies mentioned above being published, we did know that COVID-19 leads to adverse events, including acute respiratory distress syndrome and even death. When in any individual, a hyper inflammation has been developed, their summation as a multi-system inflammation, with the aid of cytokines, has no doubt contributed to the progression of COVID-19. The role of the macrophage population in such a scenario is of high importance as exacerbating or even initiating lung inflammation. Studies have provided evidence of the monocyte/macrophage population being transformed into a different one. Blood monocytes become larger and more complex in patients with COVID-19, and such (atypical) monocyte populations correlate with the severity and criticality of COVID-19. Interestingly, the phenotype of macrophages could predict the behavior of the disease. Patients with severe COVID-19 display an increased number of macrophages, in particular monocyte-derived macrophages that express Ficolin 1 (FCN1) and pro-fibrotic macrophages that represent secreted

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phosphoprotein 1 (SPP1) in the bronchoalveolar lavage fluid. Eventually, SARS-CoV-2 (the causative agent of COVID-19)-positive macrophages have shown the ability to not be confined to the lung but travel through the human body. They can occur in tissues other than the respiratory system, including mediastinal lymph nodes and the intestinal tract, explaining gastrointestinal symptoms of the disease as well.

Neopterin is a marker of cell-mediated immunity and inflammation elicited when encountering high-stress challenges. For example, in birds, heat may be such a stressor that it has been shown to increase neopterin levels (5). Exercise-induced systemic inflammation also appears to largely raise neopterin levels (6) as a strategy to preserve metabolism in platelets. It has been shown that such a response increases with the level of exercise intensity and decreases in athletes compared to non-athletes (7). Noteworthy to mention is that among about 1900 people who went back to the gym, only one developed COVID-19. This supports the effect of exercise. Moreover, olfactory dysfunction, which has been associated with increased neopterin levels, occurs in people with COVID-19, and its occurrence would predict a milder course of disease (8). On the other hand, people with severe COVID-19 show extremely elevated neopterin levels along with thrombocytopenia (9). So, an important element of the success of COVID-19 lies in hindering the body's response, which utilizes neopterin to compensate platelets. Taken together, it can be concluded that while the initial increase in neopterin represents the body's defense in mild cases, its accumulation in severe cases goes hand in hand with lung toxicity. Such a double-edged role of neopterin was previously described in bacterial infections where neopterin started to produce cytotoxicity at alkaline pH (pH 7.5). During the pandemic, the use of proton pump inhibitors, which promote alkalinization, has been associated with an increased risk of COVID-19. Lastly, the activated indoleamine (2,3)-dioxygenase (IDO) pathway mediates tryptophan degradation accompanied by neopterin production upon IFN-γ induction. There is evidence that bats served as an animal reservoir of SARS-CoV-2 and adopted modifications in the IDO pathway, thereby supporting their longevity. In humans, healthy aging is associated with increased neopterin levels and tryptophan degradation. So, the fact that older adults appear more vulnerable to COVID-19 than younger individuals is a reflection of an unhealthy aging trend.

In summary, while protocols to enhance neopterin may help to prevent COVID-19, anti-neopterin antibodies may be useful in cases of severe COVID-19 when neopterin is not further working for the host. For the former purpose, neopterin can be isolated from larvae of bees, worker bees, and royal jelly. For the latter purpose, fowls and their egg yolk can be used for active immunization and the production of anti-neopterin antibodies.

References

1. Carmona-Martínez V, Ruiz-Alcaraz AJ, Vera M, Guirado A, Martínez-Esparza M, García-Peñarrubia P. Therapeutic potential of pteridine derivatives: A comprehensive review. Med Res Rev 2019;39:461-516.
2. Saghazadeh A, Rezaei N. Implications of Toll-like receptors in Ebola infection. Expert Opin Ther Targets 2017;21:415-25.
3. Edén A, Kanberg N, Gostner J, Fuchs D, Hagberg L, Andersson LM, et al. CSF biomarkers in patients with COVID-19 and neurological symptoms: A case series. Neurology 2021;96:e294-300.
4. Ozger HS, Dizbay M, Corbacioglu SK, Aysert P, Demirbas Z, Tunccan OG, et al. The prognostic role of neopterin in COVID-19 patients. J Med Virol 2021;93:1520-5.
5. Marimuthu S, Selvam R, Kaninathan A, D'Souza P (2020) Effect of dietary supplementation of phytogenic feed additive on performance traits, serum neopterin, and cutaneous basophil hypersensitivity response in heat-induced stress model of broiler chickens. J Adv Vet Anim Res 2020;7:141-7.
6. Dantas de Lucas R, Caputo F, Mendes de Souza K, Sigwalt AR, Ghisoni K, Lock Silveira PC, et al. Increased platelet oxidative metabolism, blood oxidative stress and neopterin levels after ultra-endurance exercise. J Sports Sci 2014;32:22-30.
7. Can S, Demirkan E, Avcı E. The effect of exercise on serum Homocysteine, Adma, Neopterin and oxidative stress levels in Young male athletes. Int J Appl Exerc Physiol 2018;7:17-29.
8. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. Int Forum Allergy Rhinol 2020;10:821-31.
9. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 2020;506:145-8.