

The rediscovery of hydroxychloroquine in allergic diseases in the COVID-19 era

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To the Editor

The outbreak of coronavirus disease 2019 (COVID-19) in northern Italy has not only radically changed our everyday life and health organization but also forced us to rely on different classes of old and new drugs to contain the SARS-CoV-2 symptoms. My colleagues and I work at the Policlinico Hospital of Modena in Emilia-Romagna, the region with the second highest number of COVID-19 cases in Italy. The Italian National Institute of Health reported 168,941 laboratory-confirmed cases in Italy on April 16, and 21,486 of them were in Emilia-Romagna.

Given the lack of specific antiviral therapies against COVID-19, current treatments mainly focus on symptomatic and respiratory support, even though several compounds are being investigated for the treatment of this life-threatening disease, such as hydroxychloroquine (HCQ). To date, in selected cases at high risk of infection, the use of HCQ may be indicated for prophylactic purposes [1].

This was the case with a 35-year-old male patient, normal weight, non-smoker, known at our clinic to have a five-year history of severe seasonal rhinoconjunctivitis from trees (cypress, plane tree, poplar, birch), weed (pellitory) and grass pollen, associated with moderate asthma. In particular, he suffers from severe episodes of asthma and rhinoconjunctivitis and dramatic worsening of respiratory symptoms in early spring when working in watermelon greenhouses, infested with pellitory, strongly limiting his work activity and requiring systemic medication (i.e. oral steroid

cycles) to attenuate symptoms. On some occasions in the past, serious worsening of the clinical condition forced our patient to seek emergency room assistance, where systemic corticosteroids and other reliever drugs were administered to control severe episodes of bronchial asthma.

During the pandemic, he continued watermelon cultivation, his main work activity, without changing his routine, because agriculture in Italy was not suspended during the lockdown. As a result he reported the appearance of sneezing, itching and tearing (Rhinitis Control Scoring System-RCSS: 14) and dry cough and wheezing (Asthma Control Test-ACT: 10) associated with poor quality of life (Rhino-conjunctivitis Quality Life Questionnaire-RQLQ: 4,6; Asthma Quality of Life Questionnaire-AQLQ: 2,1). The patient had started therapy for seasonal allergic rhinoconjunctivitis (bilastine 40 mg/die, mometasone furoate 2 sprays/die) and asthma (beclomethasone/formoterol 100/6 mcg 4 puffs/die, montelukast 10 mg/die, as needed short course oral corticosteroid).

Two weeks after the start of the above anti-allergic therapy, the patient underwent therapy with HCQ 400 mg/die as prevention for two months, because a cohabiting family member was affected by COVID-19. The patient reported rapid and progressive improvement of allergy-related symptoms and quality of life (after four weeks of HCQ treatment: RCSS: 1; ACT: 25; RQLQ: 0,2; AQLQ: 6), enough to stop nasal steroid and antihistamine therapy, ICS/LABA and leukotriene receptor antagonists, without showing symptoms even when exposed to pellitory and grass pollens. We prescribed low-dose budesonide/formoterol as needed to prevent exacerbations; however, the patient never used reliever therapy [2].

It has been surprising to note how the patient has not experienced and is not yet experiencing allergy symptoms during HCQ therapy, even though he has suspended anti-allergic therapies, and it has been sunny and slightly windy with a high pollen rate in recent weeks.

Although functional pulmonary tests were suspended for the health management reorganization during the pandemic, the significant clinical improvement of our patient prompted us to investigate the biological effects of HCQ treatment on allergic diseases. Few studies have evaluated the

effectiveness of HCQ in the treatment of inflammatory processes in which mast cells play a key role, as in the case of allergic diseases.

Our reflection begins with a pioneering study from 1989, where it was shown that the pretreatment of rat mast cells with chloroquine (10-1000 $\mu\text{mol/L}$) reduced their ability to degranulate and produce prostaglandins D₂, resulting in the inhibition of phospholipase A₂ and histamine activity [3].

Moreover, it has also been shown *in vitro* that prolonged treatment with HCQ for three to five weeks on human mast cells leads to decrease the intracellular expression level of CD63 and to modify the expression pattern of CD63. Thus, HCQ treatment does not alter intracellular levels of tryptase and chymase as detected by flow cytometry, but dramatically decreases tryptase enzymatic activity and the expression of key mast cell mediators, such as IL-8 and GM-CSF [4].

These results were also confirmed by Charous et al. They reported the antiallergic effects of HCQ in terms of selective and profound inhibition of IgE and improved airflow in subjects with moderate symptomatic asthma. In fact, antimalarials seem to inhibit IL-4-driven IgE synthesis of human peripheral blood lymphocytes, suggesting that HCQ may decrease bronchial inflammation by reducing the IgE involved in its pathogenesis. It has also been shown that block histamine induced bronchoconstriction and reproducibly decreased antigen-induced bronchoconstriction in animal models, suggesting potential utility in the treatment of asthma [5].

In light of these clinical observations and the potential immuno-pathological action of HCQ, as well as its tolerability, rare toxicity, inexpensive cost and immunomodulatory properties, it makes sense to investigate the possible role of HCQ for the control of severe allergic diseases in selected cases.

Prospective clinical trials are needed to further evaluate the use of HCQ in this challenging field.

Conflict of interest

The authors declare they have no conflicts of interest.

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