



Fungistatic effect of hydroxychloroquine, lessons from a case



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ABSTRACT

A 50-year-old male was prescribed with hydroxychloroquine (HCQ) after osteoarthritis was diagnosed. He had an old nail infection of *Aspergillus niger*. A remarkable improvement of the symptoms of fungal nail infection was seen after about four weeks of treatment with HCQ. It was very hard to detect the symptoms in the end of the second month of the treatment, both in the finger and toe nails. The symptoms were clearly recurred after HCQ was discontinued.

1. Introduction

Hydroxychloroquine (HCQ) is one of the first-line disease-modifying anti-rheumatic drugs (DMARDs). In addition to this FDA-approved indication, it has several other labeled and unlabeled indications, including malaria, lupus erythematosus, porphyria cutanea tarda (PCT), chronic ulcerative stomatitis, hepatic amoebic abscess, refractory chronic urticarial, Sjögren's syndrome, granuloma annulare, erosive lichen planus, frontal fibrosing alopecia, necrobiosis lipoidica, chronic actinic dermatitis, actinic reticuloid, actinic prurigo, epidermolysis bullosa, Kikuchi–Fujimoto disease, graft-versus-host disease, chronic erythema nodosum, morphea and systemic sclerosis, and pemphigus vulgaris [1]. However it is not indicated in any form of osteoarthritis [2]. Generally, HCQ is considered as a safe and well-tolerated drug. A small percentage of the patients have reported tinnitus and nerve deafness after high accumulative dose and prolonged exposure to HCQ [3].

HCQ has shown some antiviral, antibacterial and antifungal effects. *In vitro* antifungal effects of HCQ have been reported mainly in intracellular fungi such as *Histoplasma capsulatum* and *Cryptococcus neoformans* [4] and the stipulated mechanism is either pH-dependent iron deprivation [5] or direct toxicity by increasing the phagolysosomal pH, which finally suppresses the growth of intracellular pathogens. Anyway, this effect is mediated by immune system, particularly macrophages, *via* alkalisation of phagolysosomes for intracellular bacteria and fungi [6].

2. Case

A 50-year-old male was prescribed with HCQ 200 mg/day by a rheumatologist, after osteoarthritis was diagnosed. He was complaining of pain, stiffness and tenderness in the distal joints of fingers and

knees. He was generally healthy, except for an old fungal infection of the fingernails, reportedly by *Aspergillus niger*, since 12 years ago. He had tried a 3-month course of fluconazole at that time, and a 42-d course of terbinafine one year later; both attempts failed after apparent improvement in the first few months of treatment. He had decided to restart a 90-d course of terbinafine about six months ago, after he noticed that the toenails were also involved. He had taken the precaution of postponing the terbinafine course, because he should start HCQ at the same time for osteoarthritis. The patient was surprised when he noticed a remarkable improvement of the symptoms of fungal nail infection after about four weeks of treatment with HCQ 200 mg/day, despite taking no antifungal medicine prior or during this treatment course. It was very hard to detect the symptoms in the end of the second month of the treatment, both in the finger and toe nails. In the middle of the sixth month of treatment, he referred with the complaint of persistent tinnitus and a slight hearing loss. HCQ was stopped and the symptoms of fungal nail infection were clearly recurred two to three weeks later. After another three weeks, about 20% of the left thumbnail plate and some other nails (to less extent) were discolored and separated from the nail bed (Fig. 1). Tinnitus was still persisting, six months after HCQ was discontinued..

3. Discussion

In vivo fungistatic or fungicidal effect of HCQ on nondermatophytic molds has not been documented so far. The suppression of fungal nail infection during six months of HCQ therapy, as well as the recurrence of the infection, after HCQ was stopped, could be a sign of fungistatic effect of HCQ. If further *in vitro* and *in vivo* investigations confirm such an effect, then other mechanisms should be stipulated, different from current immune phagocytosis-mediated theories to explain the effect. This is because *Aspergillus spp.* is not intracellular. A major *in*

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Fig. 1. Recurrence of onychomycosis two weeks after HCQ discontinued.

vitro study reported both direct and immune-mediated antifungal effect of chloroquine (CQ) [7]. According to this study a direct antifungal effect of CQ on both *A. fumigatus* and *A. nidulans* was found. *A. fumigatus* found to be more susceptible than *A. nidulans* to CQ, and this difference was even more pronounced in an alkaline environment. The second finding was increased antifungal activity of healthy and chronic granulomatous disease polymorphonuclear cells (CGD PMNs) by CQ. Finally, it was observed that CQ decreases both LPS-induced and *A. fumigatus*- and *A. nidulans*-induced release of TNF- α and IL-1 β by healthy and CGD PBMCs.

There has been an increasing trend towards *Aspergillus* infections in the past few decades. It is illustrated in a huge Japanese survey that reports *Aspergillus* spp. was involved in an average of 23% of deaths due to fungi in the 1970s, 27% in the 1980s, and 36% in the 1990s [8]. Considering the fact that the whole-genome sequence data of *Aspergillus fumigatus* has been identified recently, finding the novel antifungal drugs and mechanisms is a promising area of research.

In case further studies prove the direct fungistatic effect of HCQ, its mechanism would definitely be different from macrophage-mediated antifungal and antibacterial effect, which affect the intracellular microorganisms only. Up to now, six different targets have been proposed for antifungal drugs: fungal cell wall (target for echinocandins and nikkomycins), membrane phospholipid bilayer, with intercalated enzyme proteins and ergosterol molecules (target for polyenes), sterol synthesis at the endoplasmic reticulum (target for azoles, allylamines and phenyl-morpholines), DNA and RNA synthesis (targets for flucytosine), microtubule assembly (target for griseofulvin), and finally protein synthesis (target for sordarins) [9]. *Aspergillus* is a mold, hence

fungal cell wall may not be considered as a possible target for HCQ. Cellular machinery (such as topoisomerases that belong to the nuclear DNA replication and RNA transcription machinery) and signaling pathways (such as protein kinase C1-dependent cell wall integrity pathway (CWIP), targets of rapamycin (TOR) signaling pathway and protein kinase A (PKA) signaling pathway) are likely targets of HCQ [10].

Conflict of Interest

There has been no any funding or conflict of interest for this report.

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