

Review

Multiple Benefic Effects of the Systemic Exposure to the Hydroxychloroquine Sulfate

Aida (Pancă) Geamănu¹, Alina Popa-Cherecheanu¹, B. Marinescu², D.C. Geamănu³, Liliana Voinea¹

¹Ophthalmology Department, "Carol Davila " University of Medicine and Pharmacy, Bucharest

²"Victor Babes" National Institute of Pathology, Bucharest

³"Foisor" Traumatology and Orthopedics Clinical Hospital, Bucharest

REZUMAT

Efecte benefice ale expunerii sistemice la hidroxichlorochină

Hidroxichlorochina Sulfat (HCQ) este un analog de clorochină foarte eficient și extrem de întrebuițat în tratamentul lupusului, poliartritei reumatoide, a altor afecțiuni inflamatorii și dermatologice. Lucrarea își propune o trecere în revistă a efectelor multiple datorate expunerii sistemice la HCQ și posibilul potențial terapeutic al acesteia pentru multe alte afecțiuni cronice. Rapoarte recente au evidențiat efecte clinice relevante ale hidroxichlorochinei la pacienți cu alte afecțiuni decât cele reumatologice cum ar fi: boli infecțioase, hiperglicemie sau diabet zaharat, dislipidemia, coagulopatia, afecțiuni maligne. Studii noi sugerează chiar posibilitatea prevenirii degenerescenței maculare legate de vârstă la pacienții cu poliarită reumatoidă în tratament cu HCQ. Mecanismele de acțiune responsabile pentru aceste efecte sunt date de alterarea semnalizării la nivelul receptorilor celulari, modificări în post-glicozilarea agenților infecțioși, alterarea mediatorilor inflamației iar multe dintre aceste căi sunt posibil dependente de schimbările induse de HCQ în aciditatea intracelulară.

Cuvinte cheie: hidroxichlorochina, afecțiuni non-reumatice, efecte benefice

ABSTRACT

Hydroxychloroquine sulfate is an effective analogue of chloroquine, widely used to treat lupus, rheumatoid arthritis and other inflammatory and dermatologic conditions. The objective of this review is a better understanding of the multifaceted effects of systemic exposure to hydroxychloroquine (HCQ) and its possible therapeutic effect for many chronic diseases. Recent reports have shown the clinical effects of HCQ in

Corresponding author: Aida Geamanu, MD, Assistant Professor
University Emergency Hospital Bucharest
169 Independentei Street, District 5, 050098, Bucharest, Romania
e-mail: dr.aidageamanu@gmail.com

patients with non-rheumatic conditions such as : infectious diseases, hyperglycemia or diabetes mellitus, dyslipidemias, coagulopathies and malignancies. New studies reported even the probability of age related macular degeneration prevention in patients with systemic lupus erythematosus and rheumatoid arthritis using HCQ. Mechanisms of action responsible for these effects include altered signaling through cellular receptors, post-glycosylation changes of infectious agents, alterations in levels of inflammatory mediators and many of the action pathways are likely dependent on drug - induced changes in intracellular acidity.

Key words: hydroxychloroquine, non-rheumatic conditions, benefic effects

INTRODUCTION

In the twentieth century, the widespread use of quinacrine by the U.S. military as malaria prophylaxis was accompanied by other observations suggesting efficacy for treatment of rheumatologic diseases [1].

During the 1950s, the hydroxychloroquine (HCQ) derivative of quinacrine showed a favorable usage profile with less eye toxicity than chloroquine itself, and the use of this agent in the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) has become common. In RA, HCQ is usually a component of a drug combination, including triple-drug therapy with methotrexate and sulfasalazine, a formula which was claimed as a safe alternative, well tolerated compared to expensive biological therapies [2].

Efficacy in SLE has long been recognized, especially for cutaneous manifestations [3,4], but other components of this disease, including serositis, arthritis and hematologic abnormalities are also improved by treatment with HCQ [5]

While the use of HCQ in renal SLE has not been supported as first-line therapy, recent evidence suggest that the use of HCQ may retard renal damage [6], its benefic effect in patients with membranous lupus nephritis [7], significantly lowers rates of developing end-stage renal disease [8], improving overall survival and lower rates of infection [9].

HCQ is safe to use during pregnancy and cross-sectional analyzes suggest that it may reduce the risk of fetal cardiac abnormalities in mothers with SSA / SSB autoantibodies [10,11]. Increased recognition that cardiovascular disease is a cause of premature morbidity and mortality in RA and SLE has also led to an increased interest in the treatment with HCQ, which has a beneficial cardiovascular profile [12].

These recent breakthroughs have led to a

renewed interest in this drug, suggesting that all patients with SLE, including children, should be treated with HCQ, regardless of disease manifestations [13].

Moreover, previous observations, some of them decades old, regarding actions of HCQ that correlated with lower risks of blood clots and improvement in the quantity of lipids, allowed the acknowledgement that RA and SLE are associated with increased risk of cardiovascular events and anti-phospholipid antibodies are responsible for most of the thrombotic events in SLE.

Diseases and conditions other than those for which rheumatologic clinically relevant effects of HCQ were reported, were the following: antimicrobial effects, hyperglycemia or diabetes mellitus, dyslipidemia, coagulopathy, malignancies [14]. Recent studies suggest even the hypothesis of age-related degeneration prevention observed at RA cases in HCQ therapy [15].

Antimicrobial effects

HCQ was initially used as antimalarial agent, and therefore it is not too surprising that this drug has been shown to offer benefits in other types of infections. Thus it is of interest that treatment with HCQ of patients with autoimmune diseases has been associated with lower risk of infections. In a study of over 200 patients with lupus nephritis, in which antimalarials were used before establishing this diagnosis, showed significantly fewer infections than those who had not received treatment with one of these drugs [8].

Alkalinisation of acidic intracellular vesicles by HCQ and chloroquine was postulated to be responsible for inhibitory effects on the growth of intracellular organisms, including bacteria and viruses [16]. Reducing the viral load in HIV infection is considered to be due to disruption of post-translational glycosylation of the viral envelope

protein gp120, resulting in decreased infectivity of the viral particles that are produced [17]. A similar effect has been observed on other viruses, including hepatitis C [18].

Diabetes mellitus

Antimalarials act on glucose metabolism and can prevent or delay the onset of diabetes. This hypothesis is based on the following observations: a) reduced blood glucose is recognized as a side effect of treatment with antimalarials and b) HCQ has been used with good results in combination with traditional drugs to regulate glucose level in patients with type II diabetes. Dr. Wasko said: "These findings have potentially far-reaching significance, as this drug may have a role in preventing type II diabetes in the general population". A controlled clinical trial of HCQ in patients with diabetes, published more than twenty years ago, demonstrated that insulin requirements were reduced by 30% in patients receiving relatively high-dose HCQ (600 mg/day) [19]. Serum glucose and glycosylated hemoglobin were significantly lower in SLE patients taking HCQ than in those who were not on this drug. It was also observed a tendency of reducing insulin resistance in patients with SLE.

The improvement in insulin sensitivity was demonstrated in one small prospective study of 13 obese (BMI \geq 30), non-diabetic subjects who did not have RA and any other inflammatory or autoimmune diseases [20]. Treatment with HCQ for 6 weeks resulted in a significant improvement in insulin sensitivity.

Inflammatory markers such as CRP and IL-6 did not show any changes, suggesting that the effect on glucose homeostasis was independent of inflammatory pathways. Mechanisms or cellular pathways, which are responsible for HCQ effects on glucose metabolism, may involve effects on intracellular handling of insulin. In the related drug chloroquine, there is evidence of reduction the insulin degradation in human adipose tissue and this effect is associated with changes in the activity of lysosomal enzyme [21].

Dyslipidemia

Another factor related to reduction of cardiovascular risk by treatment with HCQ is the generally beneficial effect on lipid profile, which has been known for over two decades [22].

The apparent reduction of total cholesterol may

result from reduced synthesis, increased clearance or increased oxidation triggered by the inflammatory process. Alternatively the presence of circulating autoantibodies to VLDL and LDL in active RA may be responsible. There may also have pre-atherogenic effects on the vascular wall by forming immune complexes [23].

It has been suggested that treatment with chloroquine may lower cholesterol by inhibiting the proteolysis of intracellular cholesterol esters leading to increased LDL receptor values [24].

A recent prospective study examined effects of HCQ on lipoprotein profiles in 24 patients with SLE. After only 3 months of therapy, significant decrease in levels of total cholesterol and low-density lipoprotein (LDL) was observed [25].

Chloroquine and hydroxychloroquine have shown a benefic effect in decreasing atherosclerosis risk and morbidity in subjects with LES receiving antimalarial therapy.

Coagulopathy and thrombosis

An apparent effect of HCQ to reduce the number of thromboembolic events has been recognized for more than two decades [28]. Charnley reported in 1979 on the utility of HCQ as prophylaxis in preventing significant thrombotic events in the post-operative period after total hip arthroplasty [29].

In a group of patients receiving HCQ per os (doses between 600 - 1200 mg) before and after major surgery, the incidence of deep venous thrombosis at the inferior member, as measured by iodine-125-tagged fibrinogen scanning and venography, has been reduced to 5% compared with the incidence of 16% in a similar untreated group of patients. Though the increased doses could not be maintained for a long period of time due to retinal toxicity risk and HCQ was replaced with the more effective heparin.

Hematological mechanisms involved in the thrombotic effect are: decrease in red blood cell formation, decreased viscosity and platelet aggregation [30].

HCQ cancels platelet aggregation induced by antiphospholipid antibodies, cuts the link between anti- β 2-glycoprotein and phospholipid and even protects the "shield" annexin A5 anticoagulant by disrupting to the antiphospholipid antibodies [31].

Worth mentioning that the benefic effects of this drug (antithrombotic, antiagregant) have no other effect on the bleeding time [30].

Malignancies

A protective effect of HCQ therapy on the risk of developing malignancies in SLE has been suggested by some observational studies [32].

The incorporation of antimalarials, including HCQ chemotherapeutic regimens has become a new approach to oncology, based on the hypothesis that the lysosomal actions of these drugs may enhance responses to standard chemotherapeutic agents.

The theory behind these approaches in cancer therapy involves inhibition of autophagy by the anti-malarial drugs which sensitizes malignant cells to the anti-proliferative effects of chemotherapeutic agents. Even rheumatoid synovial cells are susceptible to the apoptotic effects of HCQ, an effect that was associated with activation caspase-3 [14].

Age related macular degeneration

Age-related macular degeneration (AMD) is a multifactorial, progressive, degenerative disease of the macula, retinal area responsible with central and colored vision which in advanced stages leads to blindness (Fig. 1). In elderly, AMD is the main cause of blindness and about 8 mil cases, older than 55 develop intermediate and advanced stages, in the U.S. only [33].

This macular disorder can have different clinical forms. Drusens, extracellular lipid deposits localized between the retinal pigment epithelium and Bruch's membrane are the signs of the early / intermediate forms and it develops minimal disorders of the visual acuity (Fig. 2a).

A large amount of subjects with intermediate stage progresses to the advanced one. This evolutionary stage includes forms of: a) geographical atrophy and b) neo-vascular/exudative/wet AMD (Fig. 2b) and these can co-exist at same eye, probably, because they share the same risk factors.

Early, intermediate and geographical atrophy forms constitute the atrophic/dry AMD, a frequent clinical aspect of this macular affection.

Although the pathophysiology mechanisms remain uncertain, different studies suggest that local chronic inflammation is responsible for the disease progression [34].

Risk factors includes: age >65 yrs, familial history, Caucasian race, smoking, obesity and low diet in fruits and vegetables, cardiovascular disease (hypertension), dyslipidemia.

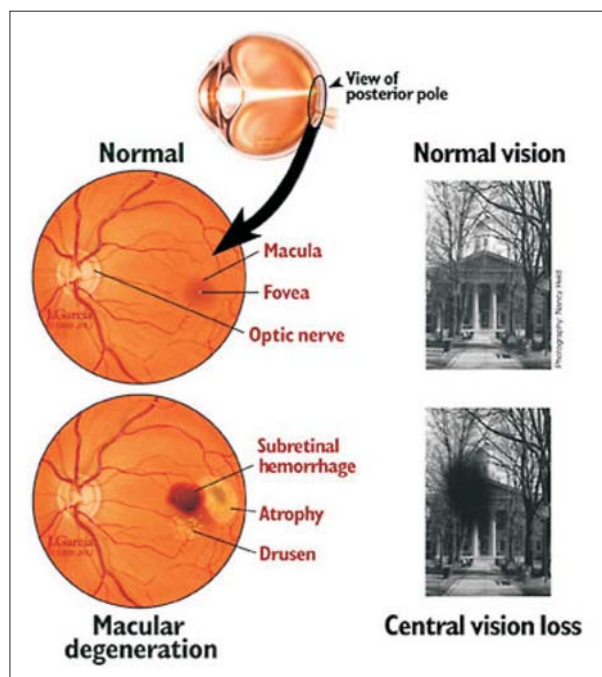


Figure 1. The fundus of a normal eye (top) and the characteristic findings of age-related macular degeneration (AMD) with specific central vision loss (bottom) [35].

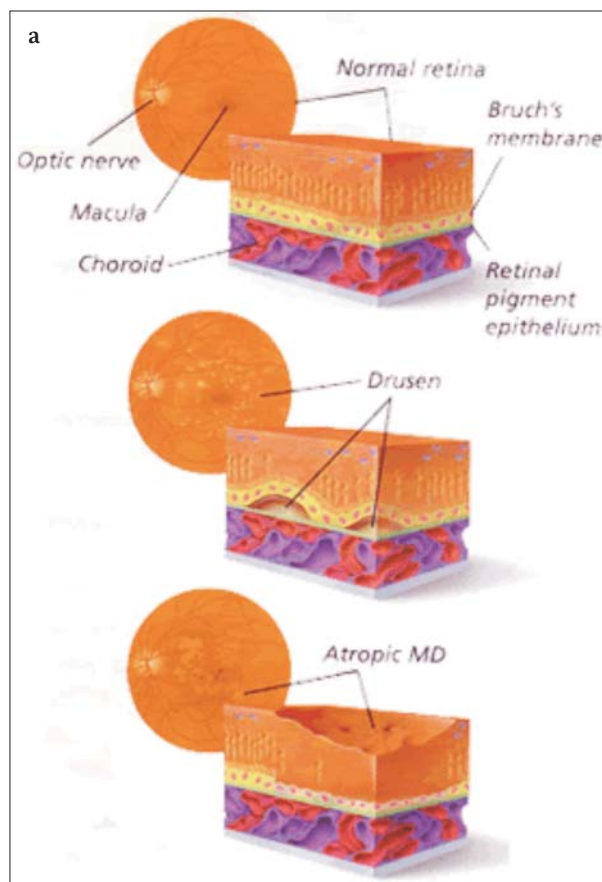


Figure 2a. Atrophic/dry AMD with extracellular lipid deposits (drusen) in the space between the retinal pigment epithelium and the Bruch's membrane [36].

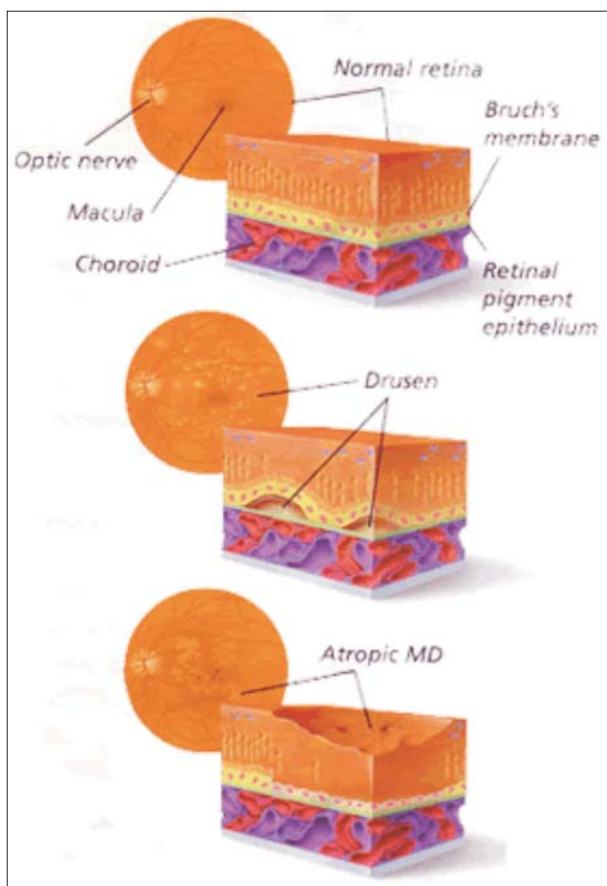


Figure 2b. Exudative/wet AMD due of the neovascularization growth with blood leakage in the subretinal space, under macula [37].

A recent retrospective study published in 2012 on 27 rheumatoid arthritis subjects under treatment with HCQ has associated increasing thickness of the external retinal layer (Bruch's membrane and retinal pigment epithelium) measured by the optical coherence tomography (OCT) compared to the control group of healthy cases [15].

This data could explain the protective effect of the HCQ to the AMD but, future thorough studies are necessary to establish the clinical implication of this hypothesis and specific effect of the hydroxychloroquine in the age-related macular degeneration.

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