Seminars in Arthritis and Rheumatism 43 (2013) 264–272

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Multifaceted effects of hydroxychloroquine in human disease ☆, ☆☆, ★

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ARTICLE INFO

Keywords:
Hydroxychloroquine
Antimalarials
Diabetes mellitus
Coagulopathy
Dyslipidemia
HIV infection
Apoptosis

ABSTRACT

Objectives: Hydroxychloroquine (HCQ) is a widely used medication for the treatment of rheumatoid arthritis and systemic lupus erythematosus. An increasing body of evidence supports actions of this drug that are not directly related to its immunosuppressive or anti-rheumatic properties. The objective of this systematic review is to characterize the spectrum of conditions that might be responsive to treatment with HCQ.
Methods: PubMed was searched using the MeSH for HCQ with relevant subheadings and the limits of human topics and English language. Four-hundred and fifty-six abstracts from this search were examined individually to exclude those that were not focused on the objectives of this review. The resulting 76 articles were grouped according to topic areas and reviewed in detail.
Results: HCQ has been reported to have therapeutic effects in a wide array of conditions, including diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases and malignancies. Mechanisms of action responsible for these effects likely include altered signaling through cellular receptors, post-glycosylation modifications of infectious agents, changes in levels of inflammatory mediators and inhibition of autophagy. Many of the pathways are likely dependent on drug-induced changes in intra-endosomal acidity.
Conclusions: The use of, and interest in, HCQ has spread into many areas of medicine. Actions of this drug may be directly beneficial to patients with non-rheumatic conditions such as diabetes mellitus or viral infections. Further understanding of underlying mechanisms has potential to reveal modifiable pathogenic pathways that might elucidate approaches to the design of more effective therapeutics for many chronic diseases.

Introduction

Drugs derived from cinchona bark have been used for centuries to treat maladies including malaria [1]. In the twentieth century, the widespread use of quinacrine by the US military as malaria prophylaxis was accompanied by other observations suggesting efficacy for rheumatologic conditions [2]. During the 1950s, the hydroxychloroquine (HCQ) derivative of quinacrine showed a more favorable usage profile with less eye toxicity than chloroquine itself and the use of this agent for treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) became common. In RA, HCQ is usually a component of medication combinations, including triple-drug therapy with methotrexate and sulfasalazine, a regimen that has been advocated as a safe, well-tolerated alternative to more expensive biologic therapies [3,4]. Efficacy in SLE has long been recognized, especially for skin manifestations [5–7] but other components of this disease including serositis, arthritis and hematologic abnormalities also are improved by treatment with HCQ [8]. While the use of HCQ in renal SLE has not been advocated as primary treatment, recent evidence suggests that use of HCQ can retard renal damage [9] and patients who have been treated with HCQ have significantly lower rates of developing end-stage renal disease [10]. Even patients with membranous lupus nephritis show benefits of HCQ [11]. Furthermore, the use of HCQ in SLE patients is associated with improved overall survival [12], decreased accrual of damage [13,14] and lower rates of infection [15]. Other data suggest that onset of SLE may be delayed if HCQ is given in preclinical stages [16]. Discontinuation of HCQ is associated with an increased risk of flares in SLE disease activity [17,18]. HCQ is safe to use during pregnancy and cross-sectional analyses suggest that it can reduce the risk of fetal cardiac abnormalities in mothers with SSA/SSB autoantibodies [19,20]. Increased recognition that cardiovascular disease is a

☆ M.S. was supported by a grant from the Research and Education Foundation of the American College of Rheumatology.
☆☆ N.J.O. was supported in part by a CURE grant from the State of Pennsylvania Department of Health.
★ N.J.O and D.R.K. were supported by NIH/NIAMS P50 AR055503.
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http://dx.doi.org/10.1016/j.semarthrit.2013.01.001

cause of premature morbidity and mortality in RA and SLE has also led to interest in HCQ, which has a beneficial cardiovascular profile [21].

These recent insights have led to renewed interest in this old drug, with some suggesting that all patients with SLE, including children, should be treated with HCQ, regardless of disease manifestations [1,22–24].

Other observations have expanded the scope of diseases or conditions that might be favorably impacted by treatment with HCQ beyond rheumatologic diseases. This in itself is not an entirely new observation, and a previous review of this subject noted several conditions, including hyperlipidemia, for which the strength of evidence for beneficial effects of chloroquine or HCQ was quite strong [25]. While some areas of potential applicability might be thought of as predictable, such as in infectious diseases, given that the original application of chloroquine itself was for malaria, others are not so obvious. Furthermore, past observations, some of them decades old, regarding actions of HCQ that correlated with lower risks of blood clots and improvement in lipid abnormalities have taken on increasing relevance with the recognition that RA and SLE are associated with elevated risks of cardiovascular events and that anti-phospholipid antibodies are responsible for most of the thrombotic events in SLE. Several recent reports have highlighted beneficial effects in patients with hyperglycemia or frank diabetes mellitus, a new area of potential therapy. Given the heightened interest and new information, a review of the pleomorphic effects of HCQ and the wider implications for disease management is timely.

Methods

The initial MeSH search of PubMed was for hydroxycholoroquine, including all subheadings except "economics" and "history". Search results were restricted to "human" and English language. This initial search produced more than 1,300 results. A second more focused search was then done with the hydroxychloroquine MeSH but excluding the additional subheadings: "chemistry", "chemical synthesis", "isolation and purification", "urine", and the two previous exclusions. The search results were restricted to major MeSH topic and also limited for articles related to humans and in the English language. This strategy eliminated publications dealing with toxicity and dosage; isolated case reports or uses in rare conditions were then removed by inspection, and this resulted in a set of 456 articles. These abstracts were individually reviewed (by M.A.S. and N.J.O.) and 76 articles about HCQ effects in non-rheumatologic illnesses were chosen along with others that emphasized multisystem effects in diseases like RA or lupus. These articles are the focus of this review. Additional articles were added during the process of writing the manuscript, mainly using references that appeared as citations in the primary articles.

Results

HCQ is labeled for use in the treatment of RA and lupus in both discoid and systemic forms. It is also often used for treatment of associated rheumatic conditions such as Sjögren Syndrome. Evidence supporting the efficacy of HCQ in RA has been summarized in a systematic review [26] and has been shown in randomized controlled clinical trials (RCTs), some of which are listed in Table 1 [27–29]. Although it is efficacious as a single agent, HCQ has in the past decade had a more widespread use for RA in combination regimens such as in triple therapy with methotrexate and sulfasalazine, which also has been shown to be effective in RCTs [3,30]. Efficacy of HCQ in the many manifestations of lupus has been recently summarized [2]. The only RCT evidence for efficacy in SLE is derived from the Canadian study of HCQ withdrawal [18]. The relative risk of flare in this study was 2.5 times higher in patients who were changed from HCQ therapy to placebo than in the group continuing with HCQ therapy, and others have reported a similar association [31]. Other studies in SLE patients have shown decreased organ damage [13,14] and enhanced survival [12,32,33] in patients receiving HCQ. Results from one analysis suggested that early use of HCQ delays onset of systemic disease [16]. Other findings indicate efficacy for treatment of cutaneous and renal manifestations [9,11,33,34] (Table 1). Safety profiles in numerous studies suggest low rates of retinopathy, safety in pregnancy and other rare adverse effects largely limited to case reports [2,24]. These cumulative findings have led to suggestions that HCQ is a cornerstone of therapy that should be given to all SLE patients [1,24]. Evidence for the use of HCQ in treatment of primary Sjögren syndrome is less substantial, and a recent systemic review could find only small trials that did not show significant benefit [35].

Table 1
Efficacy of hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis

Condition	Efficacy measure	Type of evidence	Reference
Rheumatoid arthritis	Swollen joint count, pain and ACR20 response criteria	Systematic literature review	Gaujoux-Viala et al. [26]
	Articular indices	Controlled, double-blind trial; two dose levels all patients on HCQ	Pavelka et al. [27]
	ACR50 response	Double-blind RCT	O'Dell et al. [28]
	Pain, joint tenderness and articular index	Double-blind RCT	Nuver-Zwart et al. [29]
Systemic lupus erythematosus	Rate of flare	RCT, withdrawal of therapy	The Canadian HCQ Study Group [18]
		Longitudinal cohort study	Costedoat-Chalumeau et al. [31]
	End-organ damage	Nested case–control study	Fessler et al. [13]
		Prospective cohort analysis	Molad et al. [14]
	Survival	Prospective cohort analysis	Ruiz-Irastorza et al. [32]
		Longitudinal cohort analysis	Shinjo et al. [33]
	Delayed onset of disease	Retrospective cohort analysis	James et al. [16]
	Cutaneous features	Prospective, multicenter study	Francès et al. [34]
	Prevalence new renal disease	Inceptional cohort study	Shinjo et al. [33]
	Glomerulonephritis and damage	Prospective longitudinal cohort analysis	Pons-Estel et al. [9]
	Complete renal remission for membranous nephropathy	Observational cohort analysis	Kasitanon et al. [11]