Antimalarials for the treatment of rheumatic disease: recent advances and future use

"...antimalarials remain an important therapeutic option for patients with rheumatic disease. Further study is required to better elucidate their mechanism of action and the etiology of ocular toxicity; by doing so, we may be able to optimize antimalarial use in day-to-day practice."

KEYWORDS: antimalarials ■ chloroquine ■ hydroxychloroquine ■ rheumatic disease

Steven J Katz

562 Heritage Medical Research Centre, Edmonton, Alberta T6G 2S2, Canada

Anthony S Russell

Author for correspondence:
562 Heritage Medical Research Centre, Edmonton, Alberta T6G 2S2, Canada
Tel.: +1 780 407 6296
Fax: +1 780 407 6055
asr@gpu.srv.ualberta.ca

Antimalarial medications chloroquine and hydroxychloroquine (HCQ) have been used in the treatment of a variety of rheumatic diseases for more than 50 years [1]. First examined in the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), antimalarials continue to be used frequently in these as well as other rheumatic diseases. This is despite the fact we have seen a proliferation of newer, and more advanced disease-modifying medications, particularly in the last 15 years with the advent of the biologic era. What is it about these medications that explain their enduring utilization? The answer may be as simple as their favorable benefit-to-risk ratio. As we explain, even in the last few years alone, antimalarials have demonstrated more and more potential ancillary benefits with a very small risk of adverse effects.

HCQ and chloroquine are the most commonly prescribed antimalarials for rheumatic disease. They are similar in structure, with a hydroxyethyl group in HCQ in place of an ethyl group in chloroquine [2]. They have a slow onset of action, with an equally long half-life of 40 days. The mechanism of action classically attributed to antimalarials is an induction of a small rise in the pH of cells, so called lysosomotropic action [3]; this prompts cell dysfunction including protein processing, an important immunological event that has many downstream consequences, particularly on the adaptive immune response. They have also demonstrated negative effects on a variety of proinflammatory cytokines [4]. More recently, a potent effect of antimalarials has been theorized focusing on the innate immune system [5]. Toll-like receptors (TLRs) recognize and bind foreign materials by recognizing pathogen-associated molecular patterns on microbes that do not require a great degree of specificity but typically allow discrimination from host tissue. TLRs can be found on cell surfaces as well as intracellularly. Intracellular TLRs, such as TLR7, TLR8, and TLR9, recognize viral components, but also have the ability to recognize self nucleic acid components, which are common in autoimmune diseases, such as RA and SLE [6]. While the nucleic acid components are usually found in the extracellular environment, they can be transferred inside the cell by an interaction with an antigen-presenting cell. This interaction can lead to an innate immune response, including IFN-α, as well as further activity of dendritic and B cells. Antimalarials, through their lysosomotropic properties, may prevent this interaction by inhibition of the intracellular TLRs [7].

The common clinical uses of antimalarials have long been established [8]. They have an important role in the treatment of RA. They have also been demonstrated to be an effective treatment for cutaneous lupus and some of the manifestations of SLE; perhaps more importantly, they have also been shown to prevent more serious lupus disease activity and critical organ involvement [9]. Antimalarials traditionally play a role in the treatment of Sjogren's syndrome, although recent evidence in the literature is equivocal [10–14], and in cutaneous manifestations of a number of connective tissue diseases, including dermatomyositis. While these roles for antimalarials remain important and the backbone for their clinical use, a number of ancillary benefits have come to the forefront in the last few years.

There is growing recognition of the elevated cardiovascular risk of patients with inflammatory diseases, perhaps most evident with RA [8]. While the exact nature of this relationship

Future Medicine part of fsg

remains incompletely understood, including optimal treatment strategies, it is becoming apparent that cardiovascular risk reduction may become an important component of treatment in rheumatology patients. Fortunately, there is growing evidence demonstrating the positive benefits of antimalarials in this area. A 2010 systematic review of nine smaller prospective studies demonstrated a lipid-lowering effect of antimalarials in patients with SLE, including those requiring corticosteroids [15]. A 2011 study by Morris and colleagues reviewed 706 RA patients on HCQ with a median duration of nearly 2 years. They too demonstrated positive benefits of HCQ on total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides [16]. Antimalarials also positively affect glucose metabolism. Penn and colleagues recently reported lower serum glucose rates in RA and SLE patients on antimalarials [17] and previous studies have also demonstrated a reduction in diabetes incidence [18]. Furthermore, there is growing evidence of an overall protective effect for cardiovascular events for those patients on antimalarials. A 2011 study demonstrated a 72% risk reduction of cardiovascular events in RA patients on HCQ for more than 3 years compared with those never on HCQ and less than 3 years [19]. A 2012 case–control study by Yang and colleagues showed a marked protective effect of cardiovascular events for SLE patients on HCQ compared with SLE patients not on HCQ. Traditional cardiovascular risk factors were not found to play a significant role in this small study [20].

As we continue to learn about the growing ancillary benefits of antimalarials for our patients, the information on the safety of antimalarials also continues to broaden. A 2010 systematic review by Ruiz-Irastorza and colleagues demonstrated an overall low rate of adverse events, usually mild in nature [15]. The greatest concern for antimalarial use is its potential retinal toxicity. While it remains poorly understood why it occurs, recent studies suggest the risk remains low. Wolfe and colleagues reported an overall risk for definite retinal toxicity of less than 1%, and even less for those patients whose exposure was less than 7 years duration or a 1000 g cumulative dose [21]. New recommendations by the American Academy of Ophthalmology have brought changes to previous screening guidelines [22]. Annual ocular monitoring is not routinely recommended until 5 years of drug exposure due to the small risk of toxicity demonstrated in Wolfe's study. It is also now recommended that all patients undergo some form of objective testing, such as spectral domain-optical coherence tomography, fundus autofluorescence or multifocal electroretinogram, in addition to traditional subjective exams and automated threshold visual fields. This is despite the admission that the sensitivity and specificity of these tests to detect toxicity remains unclear and requires further study. In a 2011 paper, the same lead author recommends that a low threshold is required to detect toxicity with these objective tests and where possible, consideration to use more than one modality may be preferable [23]. The use of an Amsler grid is no longer recommended, primarily due to a perceived lack of patient understanding and ability to recognize subtle changes.

A final comment is warranted on the safety of antimalarials *in utero*. The 2010 review by Ruiz-Irastorza and colleagues demonstrated no ocular toxicity or malformations in 275 reported cases across ten studies examining antimalarial use in pregnancy for both RA and SLE [15]. A 2011 review by Abarientos and colleagues demonstrated HCQ has no effect on the rate of live birth, spontaneous abortion, prematurity and no other safety issues were identified [24]. Furthermore, no use or withdrawal of HCQ during pregnancy leads to higher lupus disease activity, which in itself can have deleterious effects on pregnancy [24]. A second 2011 study by Osadchy and colleagues reviewed the risk of ocular toxicity in 12 studies, including 588 offspring of mothers on antimalarials. Again, no fetal ocular toxicity could be identified [25].

In conclusion, antimalarials remain an important therapeutic option for patients with rheumatic disease. Further study is required to better elucidate their mechanism of action and the etiology of ocular toxicity; by doing so, we may be able to optimize antimalarial use in day-to-day practice. Regardless, despite newer and more potent therapeutic options, they continue to be a mainstay of treatment and will likely remain that way for many years to come.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Wallace DJ. The history of antimalarials. *Lupus* 5(Suppl. 1), S2–S3 (1996).

2 Sturrock R. Disease-modifying antirheumatic drugs 1: antimalarials and gold. In: *Rheumatology (4th Edition).* Hochberg MC, Silman J, Smolen J, Weinblatt ME, Weisman MH (Eds). Mosby-Elsevier, MO, USA, 433 (2008).

3 Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol. Ther.* 20(4), 160–174 (2007).

4 Jang CH, Choi JH, Byun MS, Jue DM. Chloroquine inhibits production of TNF-α, IL-1β and IL-6 from lipopolysaccharide-stimulated human monocytes/macrophages by different modes. *Rheumatology (Oxford)* 45(6), 703–710 (2006).

5 Lafyatis R, York M, Marshak-Rothstein A. Antimalarial agents: closing the gate on Toll-like receptors? *Arthritis Rheum.* 54(10), 3068–3070 (2006).

6 Hennessy EJ, Parker AE, O'Neill LA. Targeting Toll-like receptors: emerging therapeutics? *Nat. Rev. Drug Discov.* 9(4), 293–307 (2010).

7 Macfarlane DE, Manzel L. Antagonism of immunostimulatory CpG-oligodeoxynucleotides by quinacrine, chloroquine, and structurally related compounds. *J. Immunol.* 160(3), 1122–1131 (1998).

8 Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr. Opin. Rheumatol.* 23(3), 278–281 (2011).

9 A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. *N. Engl. J. Med.* 324(3), 150–154 (1991).

10 Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjogren's syndrome-associated dry eye an evidence-based review. *Ophthalmology* 118(7), 1242–1252 (2011).

11 Cankaya H, Alpoz E, Karabulut G, Guneri P, Boyacioglu H, Kabasakal Y. Effects of hydroxychloroquine on salivary flow rates and oral complaints of Sjogren patients: a prospective sample study. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 110(1), 62–67 (2010).

12 Ramos-Casals M, Tzioufas AG, Stone JH, Siso A, Bosch X. Treatment of primary Sjogren syndrome: a systematic review. *JAMA* 304(4), 452–460 (2010).

13 Rihl M, Ulbricht K, Schmidt RE, Witte T. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjogren's syndrome. *Rheumatology (Oxford)* 48(7), 796–799 (2009).

14 Yavuz S, Asfuroglu E, Bicakcigil M, Toker E. Hydroxychloroquine improves dry eye symptoms of patients with primary Sjogren's syndrome. *Rheumatol. Int.* 31(8), 1045–1049 (2011).

15 Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann. Rheum. Dis.* 69(1), 20–28 (2010).

16 Morris SJ, Wasko MC, Antohe JL *et al.* Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. *Arthritis Care Res. (Hoboken)* 63(4), 530–534 (2011).

17 Penn SK, Kao AH, Schott LL *et al.* Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *J. Rheumatol.* 37(6), 1136–1142 (2010).

18 Zhang Y, Lee AS, Shameli A, Geng X, Finegood D, Santamaria P. TLR9 blockade inhibits activation of diabetogenic $CD8^+$ T cells and delays autoimmune diabetes. *J. Immunol.* 184(10), 5645–5653 (2010).

19 Bili A, Tang X, Kirchner H, Antohe J. Prolonged hydroxychloroquine use is associated with decreased incidence of cardiovascular disease in rheumatoid arthirits patients. *Arthritis Rheum.* 63(Suppl. 10), 1168 (2011).

20 Yang L, Tao J, Tang X *et al.* Prevalence and correlation of conventional and lupus-specific risk factors for cardiovascular disease in Chinese systemic lupus erythematosus patients. *J. Eur. Acad. Dermatol. Venereol.* 26(1), 95–101 (2012).

21 Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res. (Hoboken)* 62(6), 775–784 (2010).

22 Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF. American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 118(2), 415–422 (2011).

23 Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. *Arch. Ophthalmol.* 130(4), 461–469 (2012).

24 Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. *Expert Opin. Drug Saf.* 10(5), 705–714 (2011).

25 Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed *in utero* to antimalarial drugs: review of the literature. *J. Rheumatol.* 38(12), 2504–2508 (2011).