بسم الله الرحمن الرحيم

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Evaluation of Ophthalmic Adverse Effects of Hydroxychloroquine in Pediatric Patients with Rheumatologic Diseases

Thesis

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Dedication

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List of Abbreviations

Abb.	Full term
4AQs	*4 aminoquinolines*
AUC	*Area under curve*
AVF	*Automated visual field*
BDCQ	*Bisdesethylhydroxychloroquine*
CMT	*Central macular thickness*
DCQ	*Desethylchloroquine*
DMARDs	*Disease-modifying antirheumatic drugs*
FA	*Fluorescein angiography*
HCQ	*Hydroxychloroquine sulphate*
HVF	*Humphrey visual field*
IQR	*Inter-quartile range*
IS/OS	*Inner segment/outer segment*
JDM	*Juvenile dermatomyositis*
mfERG	*Multifocal electroretinography*
NPV	*negative predictive value*
OCT	*Optical Coherence Tomography*
OCT-A	*OCT angiography*
PBMCs	*Peripheral blood mononuclear cells*
PPV	*Positive predictive value*
RNFL	*Retinal nerve fiber layer*
ROC	*Receiver operating characteristic curve*
RPE	*Retinal pigment epithelium*
SD-OCT	*Spectral-domain optical coherence tomography*
SPSS	*Statistical Package for Social Science*
TCR	*T cell receptor*
TLRs	*Toll-like receptors*

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INTRODUCTION AND AIM OF THE WORK

Cutaneous manifestations in pediatric rheumatological diseases are often a prominent or the sole features for some of them as in lupus erythematosus, dermatomyositis, and rheumatoid arthritis (Clarke and Werth, 2010). Treatment of such condition includes topical therapy as steroids and Calcineurin inhibitors and systemic therapy (biological and non-biological drugs). Systemic therapy is used when the skin lesions are widespread, scarring, or ineffective topical therapies. The most important and commonly used is oral hydroxychloroquine (Tripp and Maibach, 2006; Zhneg et al., 2017).

Hydroxychloroquine sulphate (HCQ) is mainly used in treating and preventing malaria, and recently it has new applications in diabetes mellitus, heart disease and adjunct cancer therapy (Marmor, et al., 2011). HCQ has an immunomodulatory effect on different proinflammatory cytokines as IL-6 (Wozniacka et al., 2008; Da Silva et al., 2013) through its action on Toll-like receptors (Kyburz et al., 2006; Da Silva et al., 2013). It blocks UV light in cutaneous reactions, interferes with the antigen presentation and lysosomal acidification (Ohkuma et al., 1978; Da Silva et al., 2013). Its major side effect is reversible or irreversible central visual loss (Tzekov, 2007) that is usually silent in early stages (Geamănu, et al., 2014). Accordingly, early diagnosis of toxicity and evaluation of the visual function are important

(Tzekov, 2007). Increase in the incidence of such toxicity depends on the amount of daily dose, duration of intake, concomitant liver or renal disorder and the presence of an underlying initial maculopathy (Geamănu, et al., 2014). Screening guidelines states that all patients should have a baseline ophthalmologic examination within the first year of starting the drug to document any complicating ocular conditions and to establish a record of the fundus appearance and functional status and a follow up should be done after 5 years or earlier depending on presence or absence of any of the risk factors. This should be done using automated visual fields (AVF) and Spectral domain optical coherence tomography (SD-OCT) for routine primary screening and multifocal electroretinography (mfERG). Fields potentially are more sensitive, but are subjective; while SD OCT is objective, highly specific, and generally sensitive for levels of damage (Marmora et al., 2016). mfERG had the greatest proportion of positive test results, with a sensitivity and specificity of 90% and 52%, respectively (Tsang et al., 2015).

Aim of the Work

Our study was aimed at screening for the retinal damage resulting from HCQ therapy in patients in the Pediatric age group with various rheumatologic diseases and assessing the diagnostic accuracy of the investigational methods employed.

HYDROXYCHLOROQUINE

Chloroquine was discovered in 1939 and since the 1950s, Hydroxychloroquine sulphate (HCQ) is mainly used in treating and preventing malaria (Yam et al., 2006; Chang et al., 2011; Yusuf et al., 2017) then people started to use it in treating rheumatologiacl diseases as SLE since the last century. Initially, they were used because of their efficacy on the disease's skin manifestations (Casian et al., 2018; Spinelli et al., 2018). Recently it is used in diabetes mellitus, heart disease and adjunct cancer therapy (Marmor et al., 2011).

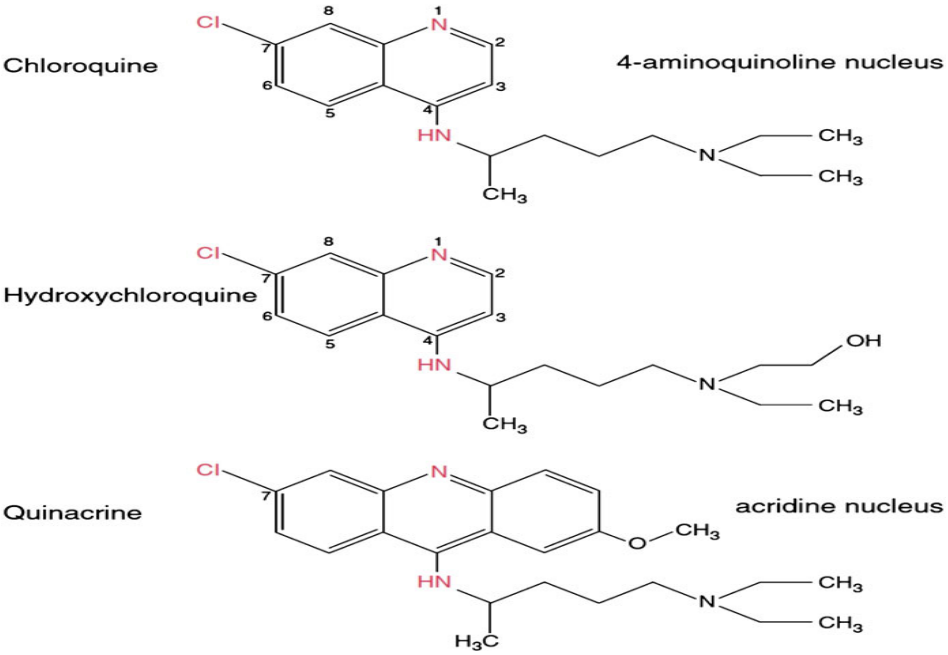

Figure (1): Chloroquine and hydroxychloroquine are 4-aminoquinolines. Quinacrine has a side chain similar to that in chloroquine, but is based on an acridine nucleus (Browning et al., 2014).

In a way to understand what Hydroxychloroquine from all sides, we will start with the chemistry of this drug. The parent molecule for the antimalarials is quinine. Both chloroquine (C 18 H 26 ClN 3) and hydroxychloroquine (C 18 H 26 ClN 3 O) are alkylated 4 aminoquinolines (4AQs). Chloroquine is 7-chloro-4(-4-diethylamino- 1- methylbutylamino) quinoline and hydroxychloroquine is its hydroxyl derivative. Chloroquine and hydroxychloroquine have molecular weights of 320 and 336, respectively. Both chloroquine and hydroxychloroquine are amphiphilic weak bases based on two fused aromatic rings having conjugated double bonds, the 4-aminoquinoline nucleus. Both drugs cross cell membranes well. Hydroxychloroquine is more polar, less lipophilic, and has more difficulty diffusing across cell membranes. The 4AQs lack the third benzene ring that is part of the acridine nucleus of quinacrine (Browning et al., 2014).

The pharmacokinetics of chloroquine and hydroxychloroquine are similar. The peak plasma concentration after an oral dose of chloroquine is 3–12 h. Thirty three to 70 % of the drug in plasma is proteinbound. There is effect of ethnicity on 4AQs pharmacokinetics but not differ to a clinically important extent between black and white patients. The average melanin content of a black person is estimated to be 1 g and for a white person is estimated to be 250 mg. Melanin interaction with 4AQs is complex which prevents formation of lamellar bodies until its binding capacity is exceeded. Chloroquine accumulates in the uveal tract of pigmented animals, but not albino animals, but