بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Possible Adverse Effects of Long-term Use of Hydroxychloroquine on Corneal Endothelium

Thesis

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List of Abbreviations

Abb.	Full term
APCs	Antigen-presenting cells
BCVA	Best corrected visual acuity
CCT	Central corneal thickness
CD	Cell density
COVID-19	Coronavirus disease 2019
CV	Coefficient of variation
HCQ	Hydroxychloroquine
IL	Interleukin
IOP	Intraocular pressure
JIA	Juvenile idiopathic arthritis
pDCs	Plasmacytoid dendritic cells
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
TLR	Toll- like receptors
TNF	Tumor necrosis factor

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INTRODUCTION

The cornea is a transparent, avascular tissue that acts as a structural barrier and protects the eye against infections. Along with the tear film, it provides proper anterior refractive surface for the eye. The cornea contributes to two thirds of the refractive power of the eye ***(Del Monte and Kim, 2011).***

The cornea is formed of six layers which are epithelium, Bowman's Layer, stroma, Dua's layer, Descemet's membrane and endothelium. Dua's layer is a well- defined, acellular layer in pre-Descemet's cornea which has gotten a great attention with the development of lamellar keratoplasty surgeries. This layer has a range of thickness from 6.30 to15.83µm ***(Dua et al., 2013).***

The endothelium is a single layer, five µm thick structure. The cells are hexagonal and metabolically active. There is an endothelial pump which regulate water content of the cornea. The lateral membrane contains the highest density of Na+ K+ATPase pump sites. The two most important ion transport systems are the membrane bound Na+ K+ ATPase pump and the intracellular carbonic anhydrase pathway. Activity of both these systems produces the net flux of ions from stroma to aqueous leaving the stroma relatively dehydrated to keep its transparency. Endothelial cell density continues to change throughout life. Human central endothelial cell density decreases at an average of approximately of 0.6%

per year in normal corneas throughout adult life. Endothelial cells compensate for this decline in cell number by polymegathism and pleomorphism as they lack the ability of regeneration ***(Rio-Cristobal and Martin, 2014).***

Hydroxychloroquine is an antimalarial drug commonly used in autoimmune rheumatological diseases such as systemic lupus erythematosus and rheumatoid arthritis as immunomodulatory drug. Despite the beneficial effect of hydroxychloroquine in preventing systemic lupus flares and reducing mortality, it has a toxic effect on retina and possibly on corneal endothelium. These effects may be related to the dose and the duration of drug therapy. There is no specific treatment for retinal toxicity other than cessation of treatment. Screening tests for retinal toxicity is important in early detection of toxicity and preventing irreversible vision loss ***(Ruiz-Irastorza et al., 2010).***

Hydroxychloroquine may precipitate in corneal epithelium in a diffuse or whorl-like pattern causing vortex keratopathy or cornea verticillata. These precipitates are usually asymptomatic. This effect is much less with hydroxychloroquine than chloroquine ***(Yam and Kwok, 2006).***

Aim of the Work

Detection of possible adverse effects of long-term hydroxychloroquine use on corneal endothelium in patients of rheumatological diseases who used the drug for at least three years.

Review of Literature

Hydroxychloroquine (HCQ) is a well-tolerated drug for various rheumatologic and dermatologic conditions. It has been used off-label as a potential therapy for the new corona virus, COVID-19, although data to support its efficacy is not sufficient due to lack of large, controlled trials (figure 1) ***(Gbinigie and Frie, 2020).***

Figure (1): Hydroxychloroquine ***(Skipper et al., 2020).***

Hydroxychloroquine is a less toxic metabolite of chloroquine which is used to treat rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren's syndrome (figure 2) ***(Jorge et al., 2018).***

Figure (2): Hydroxychloroquine chemical structure ***(Tehrani et al., 2008)***.

Its main side effects are gastrointestinal upset (vomiting, diarrhea and stomach cramps), skin rash, headache, dizziness, and ocular toxicity. Serious side effects including arrhythmia, bronchospasm, angioedema, and seizures can rarely occur. Hydroxychloroquine can adversely affect the cornea, ciliary body and retina ***(Yam and Kwok, 2006).***

This study aims at detection of possible adverse effects of hydroxychloroquine on corneal endothelium in patients received the drug for at least three years. Hydroxychloroquine is most often used for its anti-inflammatory or immunosuppressive effects in rheumatology and dermatology ***(Marmor and Hu, 2014).***

Corneal toxicity presents as intraepithelial deposition of the drug into the cornea, which rarely affect vision. These deposits accumulate in the basal layers of corneal epithelium to form a whorl-like pattern. This side effect is called vortex keratopathy or cornea verticillata (figure 3). Also hydroxychloroquine causes ciliary body dysfunction which disturbs accommodation. ***(Yam and Kwok, 2006).***

Figure (3): Corneaverticillate ***(Moiseev et al., 2018).***

Symptoms of corneal deposits includes haloes and glare which may occur in some advanced cases. These deposits appear as bilateral fine, golden brown or grey opacities in the inferior cornea that branch out of a central whorl ***(Dosso and Rungger,2007).***

The hallmark of hydroxychloroquine toxicity is bilateral pigmentary retinopathy ***(Tehrani et al., 2008)***.