Trends in Immunotherapy (2017) Volume 1 Issue 1
doi: 10.24294/ti.v1.i3.127

Editorial

Hydroxychloroquine in lupus erythematosus, a new horizon of the old drug

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CITATION

Furukawa F. Hydroxychloroquine in lupus erythematosus, a new horizon of the old drug. Trends Immunother 2017; 1(1): 99–100. doi: 10.24294/ti.v1.i3.127.

In this volume 1 issue 3, Japanese doctors present a discoid lupus erythematosus (DLE) patient well treated with hydroxychloroquine (HCQ) (Figure 1), in whom urticarial reaction was transiently worsened[1]. This case has two underlying aspects especially for Japanese doctors, which is probably shared with Asian doctors.

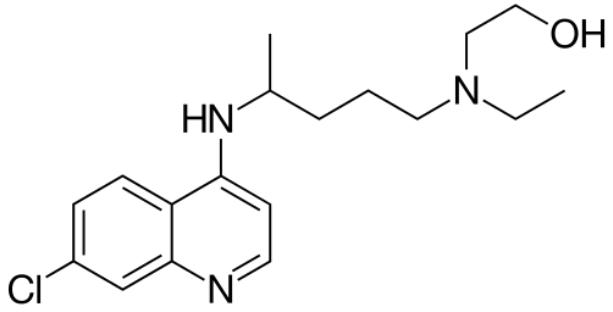

Figure 1. Molecular structure of hydroxychloroquine

First of all, antimalarials are acknowledged to be the first-line throughout the world[2,3], but Japanese physicians could not prescribe them to cutaneous lupus erythematosus (CLE) patients until 2015 because of previous medical accidents resulting in severe chloroquine retinopathy[4]. In Japan, chloroquine was approved of its use for malaria in the latter half of the 1950s, rheumatoid arthritis (RA), systemic LE (SLE), nephritis, nephrosis, and epilepsy. Case reports of chloroquine retinopathy increased after 1962 and retinopathy was described in the package insert in 1969. The drug was re-evaluated in 1972 and efficacy against malaria, SLE, and RA was reported in 1976. Chloroquine production was discontinued in 1974 because of lawsuits brought by patients who developed retinopathy.

In addition, HCQ is a first-line antimalarial therapy due to a lower incidence of retinal toxicity compared with chloroquine. Consequently, the drug became the first-line treatment for SLE and RA worldwide[2,3]. However, in Japan, HCQ followed the same fate as chloroquine even though there were no clinical experiences. Recently, nationwide clinical trials on the efficacy and safety (multicenter randomized control trial) were performed and excellent results were reported[5]. Interestingly, this report is the first clinical trial oriented for the approval because HCQ is very old and was approved in 1955 in the United States of America. Concerning the subtypes of LE, the effectiveness and safety of 30 cases treated with HCQ in Japan and responsiveness to HCQ in DLE was lower than that of acute CLE and annular erythema[6].

HCQ has numerous biological effects that are responsible for their immune-related actions in SLE and CLE. Recent advances of innate immunity and metabolic syndrome research have raised the new insights and horizons[7]. It is not clear why HCQ is effective at treating autoimmune diseases such as LE, RA, *etc.* However, it is believed that HCQ interferes with the communication of cells in the immune system. Recent studies suggest that the inhibitory effect on TNF *via* down-regulation of Toll-like receptor 7 or 9-mediated activation of the innate immune response is perhaps the most important discovery regarding their putative mechanism of action[7,8]. Some other, previously known properties,

such as antithrombotic and antilipidaemic effects, are now explained by new research[7].

Antimalarial agents have unique disease-modifying properties in SLE and newer iterations of this class of anti-inflammatory agents will have a profound effect upon the treatment of autoimmune disease. As one candidate, mast cell will be a new clue for better understanding some possibilities of the old drug[9–11].

Acknowledgment

This work was supported by a grant from the Japan Society for Promotion of Science.

Conflicts of interest

No conflict of interest was reported by the author.

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