

## Use of Hydroxychloroquine in Japan

To the Editor:

Antimalarial agents have been used for the treatment of inflammatory diseases for the last half century, with hydroxychloroquine (HCQ) being approved in the United States in 1955<sup>1</sup>. In addition to its common use in systemic lupus erythematosus (SLE), including cutaneous forms, it has also proven useful in treating rheumatoid arthritis (RA)<sup>2,3,4</sup> and Sjögren's syndrome<sup>5</sup>. In SLE, antimalarial agents have been shown to decrease disease activity and subsequent flares in both nonpregnant<sup>6</sup> and pregnant patients<sup>7</sup>. Other potential benefits include a decreased risk of infection<sup>8</sup> and thrombosis<sup>9</sup>. HCQ has been shown to exert a positive effect on overall survival<sup>10</sup>. In a large cohort of multiethnic patients with SLE (the LUMINA cohort), HCQ prevented renal and central nervous system disease<sup>11,12</sup>. Finally, a recent report suggests that maternal use of HCQ may decrease the risk of cardiac manifestations of neonatal lupus<sup>13</sup>.

Despite these benefits and its current use in over 70 countries, chloroquine and HCQ remain unavailable for clinical use for rheumatology patients in Japan. This unavailability stems from a series of lawsuits in the 1970s as a result of chloroquine retinal toxicity, which was first reported by Cambiaggi in 1957<sup>14</sup> and further confirmed by Hobbs, *et al* in 1959<sup>15</sup>. Interestingly, chloroquine was widely used in Japan for a variety of clinical indications from 1955 through the early 1970s, including malaria, RA, and SLE, as well as in diseases such as epilepsy and chronic nephritis, in which baseline risk of retinal toxicity was likely higher to begin with<sup>16</sup>. The dangers associated with chloroquine use were compounded by the absence of rigorous safety screening protocols, despite the known potential for retinal toxicity. As a result, chloroquine was withdrawn from the Japanese market in 1974.

In the last decade, the clear benefits of antimalarial agents in rheumatological diseases have been increasingly recognized, by the growing cohort of returnee patients already treated with HCQ overseas as well as US-trained rheumatologists returning to Japan for clinical practice. In 2009, an initiative began to promote the study and introduction of HCQ into clinical care in Japan, appreciating the importance of updated safety screening protocols<sup>17,18</sup>, including earlier detection of retinal toxicity with newer ophthalmologic modalities such as multifocal electroretinogram, spectral domain optical coherence tomography, or fundus autofluorescence. Given its wide use as a standard of care worldwide, there is little reason to support HCQ's continued absence from the market. Unsurprisingly, a recent small study of HCQ in Japanese patients with SLE showed benefit in cutaneous disease, arthritis, and fatigue<sup>19</sup>. To this end, 2012 will see the first clinical trial of HCQ for SLE in Japan.

We hope that an understanding of the history of antimalarial agents in Japan — a legacy that precluded the appropriate use of an efficacious therapy — will soon lead to an era of improvement of patient care, survival, and quality of life for patients with SLE in Japan.

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