

Title: Effect of hydroxychloroquine on B cell tolerance in the germinal center

Rationale SLE is an autoimmune disease mediated by antinuclear antibodies. Antimalarial agents such as hydroxychloroquine (HCQ) have been used as the first-line treatment of lupus for nearly 60 years. HCQ prevents lupus flare ups and increases the long-term survival by suppressing lupus autoimmunity but sparing normal immune functions required to protect against pathogens. However, the underlying mechanism of HCQ remains unknown. We propose that HCQ may enhance the protective mechanisms, such as B cell tolerance, to help selectively delete the autoreactive B cells in the body. In this study, we focus on the effect of HCQ on B cell tolerance in the germinal center (GC) because studies have identified somatic hypermutation in GC B cells as the major source of lupus autoreactivity. Methods NZBWF1 mice were used in this study. Serum anti-dsDNA IgGs and proteinuria were measure by ELISA and Bradford Assay resp. When the level of serum anti-dsDNA IgGs arises above 3mg/ml, the mice started to receive HCQ (2-10 mg/kg/day) by oral gavage for 4 weeks. Control mice were treated with PBS. Splenocytes were isolated for FACs analysis, GC B cells were purified for biochemical assays, and kidneys were harvested for pathology. Results Our preliminary results showed that HCQ treated mice had reduced serum levels of anti-dsDNA IgGs and proteinuria compared to the PBS treated control. Consistently, spleen weight and the proportion of GC B cells were reduced in HCQ treated mice. H&E tissue staining of kidney tissue sections are still pending results. Significance Lupus patients on HCQ usually discontinue treatment due to intolerance or HCQ-induced toxicities, resulting in frequent flares. Therefore, a new agent that targets lupus autoimmunity without affecting other organs is highly desirable. Understanding how HCQ suppresses lupus autoimmunity will help identify the new therapeutic target for developing a strategy that preserves the therapeutic effectiveness but avoids the toxicities