Comparative Safety of Therapies in Systemic Lupus Erythematosus

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KEYWORDS

• Systemic lupus erythematosus • Adverse effects • Antimalarials • Azathioprine
• Cyclophosphamide • Mycophenolate mofetil • Rituximab • Belimumab

KEY POINTS

- A wide variety of medications are used to treat systemic lupus erythematosus, depending on organ involvement and severity.
- Some of these drugs, especially immunosuppressive and cytotoxic agents, often lead to significant toxicity.
- Physicians must familiarize themselves with the adverse effects of each of these drugs and discuss them with patients to facilitate educated decision making.

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease resulting from a dysregulation of immune function. Diverse clinical manifestations may be seen, affecting virtually all organ systems.[1] For this reason, a wide variety of medications are used for treatment, depending on organ involvement and severity. Although some of these treatments are usually safe and well tolerated, others, especially immunosuppressive and cytotoxic agents, often lead to significant toxicity.

ANTIMALARIALS

Several antimalarial medications have been used to treat SLE for more than 100 years. Hydroxychloroquine (Plaquenil) is currently the most commonly used, although chloroquine (Aralen) and quinacrine (Atabrine, Mepacrine) also remain in use. Several recent studies have highlighted the many benefits of antimalarials in patients with SLE, including

- An improvement in lipid profiles[2]
- Reduction of SLE activity[3]

Disclosure: Dr Furie has served as a paid consultant to: 1) Genentech, Roche, and Biogenidec; 2) Human Genome Sciences, GlaxoSmithKline.
Funding sources: None.
Conflicts of interest: None.
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Rheum Dis Clin N Am 38 (2012) 795–807
http://dx.doi.org/10.1016/j.rdc.2012.08.009 rheumatic.theclinics.com
0889-857X/12/$ – see front matter

- Prevention of thrombotic events[3]
- Improved survival[4,5]

Although antimalarials are generally well tolerated and possess good safety profiles, they are associated with adverse events (AEs), although these are infrequent and generally mild. The most common AEs are gastrointestinal and cutaneous, whereas the most serious AE, although rare, is retinopathy. In one study comparing the toxicities associated with hydroxychloroquine and chloroquine, 28% of patients receiving chloroquine experienced AEs compared with 15% of those receiving hydroxychloroquine ($P<.00001$).[6]

Retinopathy

The risk of retinopathy (**Fig. 1**) from hydroxychloroquine is low, especially compared with chloroquine. In a study performed in Thailand, 37 of 139 patients (27%) receiving chloroquine experienced retinopathy.[7] In contrast, in a large series of 1207 patients taking hydroxychloroquine for rheumatic diseases, only 1 case of definite retinal toxicity was identified.[8] In a more recent study, definite or probable retinal toxicity occurred in 0.65% of 3995 patients taking hydroxychloroquine. Although the toxicity rate remained low with longer durations, an increase in toxicity was seen after approximately 6 years of use, or with a cumulative dose of 800 g.[9] For this reason, the American Academy of Ophthalmology recommends that all patients starting on hydroxychloroquine or chloroquine have a baseline examination within the first year of starting the drug. Annual screening should then be performed after 5 years of use in all patients, and from initiation of therapy for patients with maculopathy or unusual risk factors.[10] Recommended screening procedures include careful ocular examination, automated visual field testing, and, when available, testing with one or more objective tests of anatomic or functional damage.

Cutaneous

Cutaneous side effects are common in patients taking antimalarials. Cutaneous pigmentary changes have been found in up to 25% of patients taking these medications for more than 3 months.[11] Any of the antimalarials may produce localized blue-black pigmentation, which predominantly affects the pretibial areas, face, gums, hard palate, and subungual regions, although it has most commonly been seen with chloroquine (**Figs. 2** and **3**).[12] This effect was seen in 25 of 300 patients receiving

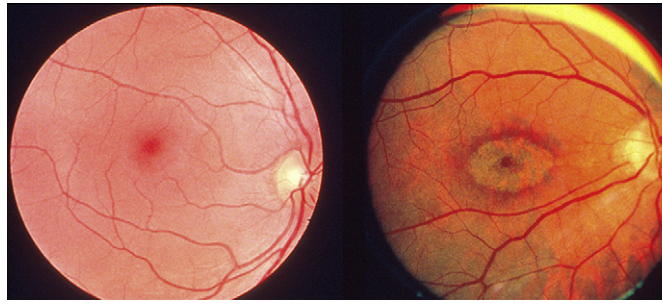

Fig. 1. Left: an early "bull's-eye" lesion resulted from hydroxychloroquine therapy. Stippled annular hyperpigmentation of the macula is seen. Right: a late lesion shows a central area of hyperpigmentation and an intermediate zone of hypopigmentation encircled by a pigmented rim, creating the characteristic bull's-eye effect. (© 2012 American College of Rheumatology. Used with permission.)