The hydroxychloroquine–interferon gamma release assay question: TB or not TB?

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Hydroxychloroquine (HCQ) is a workhorse of medical dermatology. Aside from treating malaria, it has been used to treat the spectrum of immunologically implicated dermatoses from annular elastotic granuloma to urticarial vasculitis. Most typically, it is a standard treatment for lupus erythematosus, dermatomyositis, lichen planopilaris, granuloma annulare, sarcoidosis, and reticular erythematous mucinosis.

HCQ has unique immunomodulatory properties (antithrombotic, antifibrotic, antidyslipidemic, and antihyperglycemic), allowing it be used in lieu of steroids or other immunosuppressive agents. Rare adverse effects of HCQ include blood dyscrasia and hepatotoxicity. As monitoring renal function is essential for appropriate dosing of HCQ, periodic complete blood counts and metabolic profiles are essential. Routine glucose-6-phosphate dehydrogenase deficiency testing is not recommended because hemolysis with glucose-6-phosphate dehydrogenase deficiency does not occur at the usual doses. Regarding potential retinopathy, baseline screening should be performed within the first year of treatment, with annular toxicity screening beginning after 5 years of use.[1]

According to Albert-Vega et al, "tuberculosis (TB) is among the top 10 causes of death worldwide. Active TB accounts for 5-10% of the cases and is suspected when the symptoms manifest such as a severe cough that lasts 3 weeks or longer, pain in the chest, and coughing up sputum or blood. Active TB is well managed with antibiotics when detected in an early stage. However, latent tuberculosis infection (LTBI, which presents 90-95% of the cases) lurking in the host is asymptomatic and has a high probability of being activated in a hampered immune system. The ability to detect latent TB is therefore critical in situations where patient's management implies iatrogenic immune-suppression such as chemotherapy, transplantation, or chronic inflammatory diseases."[2]

Interferon gamma release assays (IGRAs) measure a person's immune reactivity to *Mycobacterium tuberculosis*. Currently, there are 2 US Food and Drug Administration–approved commercially available tests: QuantiFERON-TB Gold test (QFT) (Qiagen, Valencia, CA) and T-SPOT.TB (Oxford Immunotec, Marlborough, MA). The advantages of both tests over tuberculin skin testing are that they only require a single patient visit to conduct the test and the results can be available within 48 to 72 hours. Excellent specificity has been described for detection of latent TB, without false-positive results in bacillus Calmette-Guérin–vaccinated subjects and with only a limited number of false-positive results due to nontuberculous *Mycobacterium*/*Mycobacterium* other than *M tuberculosis*. Disadvantages of TB IGRAs include poor sensitivity of detection of latent TB, poor reproducibility, high number of indeterminate results, and inability to discriminate between latent and active TB.[2]

Dermatologists have appropriately become accustomed to screening for LTBI in their psoriatic patients who are taking biologics, especially the anti–tumor necrosis factor-α inhibitors.[3]

On the basis of the observation that chloroquine and HCQ may inhibit production of tumor necrosis factor and interferon gamma,[4] Gaffney and Werth[5] questioned whether HCQ-treated autoimmune patients have a higher rate of indeterminate IGRAs. In this issue of the *Journal of the American Academy of Dermatology,* Gaffney and Werth have reviewed medical records of 89 patients with cutaneous lupus or dermatomyositis tested with the QFT. Patients

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were sorted into groups based on the presence or absence of HCQ use within 1 year of testing with the QFT while accounting for concomitant use of other antimalarials, prednisone, or other disease-modifying antirheumatic drugs. The HCQ group included 45 patients, and 44 patients did not use HCQ in the year before testing. The HCQ group had significantly more indeterminate QFT results (38%) compared with the non-HCQ group (6.6%) ($P < .01$).[5]

This study raises an intriguing practical question for HCQ-treated patients with an indeterminate IGRA result: do they have LTBI or not? The likelihood is that in low-risk patients, the test is falsely indeterminate. Each patient must be assessed individually; if patients are at high risk of LTBI, repeat IGRA testing, a tuberculin skin test, chest radiograph, and infectious disease consult may all be appropriate.[6] It is a question that must be answered before utilizing other immunosuppressive agents in patients with HCQ-resistant disease.

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