To the Editor:

As Brittenham\(^1\) has reviewed in detail, the use of the oral iron chelator LI has been associated with significant clinical and animal toxicity. One of the more controversial issues surrounding the human use of LI has been the possible development of autoimmune phenomena as manifested by development of autoantibodies such as antinuclear antibodies (ANA).

The Canadian group investigating LI did not describe any immunologic abnormalities in their initial report,\(^2\) but later reported positive ANA in 5 of 12 thalassemics with negative antibodies to double-stranded DNA (AdsdNA) and antibodies to histones (AHA) in all before starting LI,\(^3\) after we reported possible drug-induced lupus in a patient taking LI.\(^4\) The phase II LI trial report on 52 thalassemics in India showed no "significant toxicity" on "extensive clinical and laboratory monitoring" of several organ systems and functions.\(^5\) An update of the Indian trial\(^6\) then reported ANA-positivity in 10 of 52 (19.2%) thalassemics on LI and in 12 of 83 (14.5%) thalassemics on LI.

It is surprising that neither Al-Refai et al\(^7\) nor Agarwal et al\(^8\) mention AHA in their patients on LI who developed ANA because AHA are supposed to be specific for drug-induced lupus,\(^9\) and the triad of positive ANA and AHA, and negative AdsdNA is typical of drug-induced lupus.\(^9\)

To address the question of autoimmunity in transfusion-dependent thalassemia, we investigated 90 patients with thalassemia major for the occurrence of autoantibodies.\(^9\) ANA were detected in 7 of 27 (25.9%) patients on LI, and in 2 of 63 (3.2%) patients not on LI (\(P < .01\)). AHA were seen in 4 of 7 patients on LI with positive ANA, and in neither of the 2 not receiving LI (\(P < .03\)). AdsdNA were undetectable in all patients with positive ANA. Five months after discontinuation of LI, one of the patients with positive ANA and AHA became negative for both, and four months after discontinuation of LI, another patient with a positive ANA and a negative AHA became negative for ANA.

Our investigations show that while there is a small amount of background ANA-positivity in patients with thalassemia major, AHA are always absent. The frequency of ANA-positivity is significantly higher in thalassemics receiving LI, some of whom also have positive AHA, consistent with drug-induced lupus.\(^6\) The development of ANA may precede the development of AHA as shown by the AHA-negative patient whose ANA became negative after discontinuation of LI. While the exact mechanism and significance remain unknown, LI seems to cause significant autoimmune phenomena in humans that may be reversible if the drug is stopped early enough but may progress to symptomatic systemic lupus erythematosus (SLE). The human use of LI should be very cautious and only under careful monitoring.

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RESPONSE

Dr Mehta and colleagues raise the issue of a systemic lupus erythematosus (SLE) syndrome that might be induced by the oral iron chelator L1. This group has previously reported on a patient with thalassemia major who died when taking L1 and they suggested that an SLE-like syndrome was present. This association remains unsubstantiated. The patient died on the second day of high-dose methyl prednisolone therapy; this treatment, as Berdoukas has suggested, may have caused sudden cardiac decompenation. This is more likely to occur in a patient with pre-existing heart disease secondary to iron overload. It is also possible that septicemia may have contributed. Therefore, we agree with Berdoukas that the positive antinuclear antibody test in this patient is likely to have been incidental.

We have monitored the antinuclear (ANA) and rheumatoid (RH) factors both before and during L1 therapy in the patients we studied in our two long-term trials at the Royal Free Hospital. In the first trial of 13 patients we reported an increase in the titer of RH in two patients (1/80 to 1/160, 1/80 to 1/640) and no change in the incidence or titer of ANA. In the second trial of 11 patients there was no change in the incidence or titer of RH and a slight increase in the incidence and titer of ANA. Initially two patients were ANA positive (1/160, 1/40) and finally four patients were positive (1/320 [one patient] and 1/40 [three patients]). If only those patients with clearly positive ANA (titer >1/80) are considered, there was only a change in titer in one patient and no change in incidence. We have been prepared to measure antibodies to double-stranded DNA (dsDNA) and antihistone antibodies (AHA) in any patient developing a significantly positive ANA during L1 therapy, but no patient has developed this condition. Agarwal et al reported similar findings in earlier reports that have recently been updated. They found an increase in the incidence of positive (>1/80) ANA from an initial incidence of 11.5% (6 of 52 patients) to a final incidence of 19.2% (10 of 52 patients). There was also a slight increase in the incidence of positive (>1/80) RH from 7.7% to 11.5%. There was no anti-dsDNA positivity in any patient and AHA was not tested. In none of the above trials was there a correlation between musculoskeletal symptoms that occurred in some of the patients and the change in autoantibody status and no other evidence of SLE was observed.

None of the 12 patients studied by Olivieri et al who received L1 for up to 12 months developed positive autoantibody tests while on L1 therapy. Before the commencement of L1, three were ANA positive, three were RH positive, and two were positive for both. None of these patients developed AHA or anti-dsDNA antibody during the trial. More recently, Berkovitch et al reported knee joint pain in 3 of the 15 patients who had received L1 for 12 to 30 months. ANA converted from negative to positive in all three patients but has remained positive in only one patient despite continuation of L1. Initially, 4 of the 12 asymptomatic patients had positive ANA and one has remained positive. RH was initially positive in 5 of the 12 patients and remained positive in 4 patients. Anti-dsDNA and AHA were negative in the 15 patients throughout the trial. Fifty-three desferoxamine-treated patients with thalassemia major were also studied. Seventeen (32%) were found to have joint symptoms. Autoantibody results were obtainable on 14 of the 17 patients. Three had positive ANA (21%) and one had positive RhF (7%).

Therefore, weakly positive ANA and RhF tests are not infrequent findings in patients with thalassemia major whether they are receiving L1 or desferoxamine. In some studies there appears to be a small increase in the incidence and titer of these antibodies in a minority of patients receiving L1 with no association with other symptoms suggestive of SLE. It is clearly necessary to monitor for these autoantibodies and for other immune abnormalities in patients receiving L1 in long-term human trials. The question of whether an L1-induced SLE syndrome occurs remains unproven.

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Oral iron chelator L1 and autoimmunity [letter; comment]

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