

Absence of Transaminase Elevation During Concomitant Methotrexate and Isoniazid Therapy

To the Editor:

It has become the standard of care to screen patients for latent tuberculosis infection (LTBI) prior to initiating tumor necrosis factor- α (TNF- α) antagonists, and treat with isoniazid (INH). Unfortunately, INH has been associated with hepatotoxicity. Estimates suggest that transaminase elevations may be seen in as many as 0.1% to 10% of patients treated with INH^{1,2}. Patients with rheumatic disease may already be receiving potentially hepatotoxic medications such as methotrexate (MTX). Although the doses of MTX typically employed to treat rheumatic diseases are generally considered to be safe, mild reversible hepatotoxicity is common, and isolated cases of irreversible liver damage have been described^{3,4}. The combination of 2 potentially hepatotoxic medications raises significant concern regarding safety. We describe the results of concomitant treatment with MTX and INH on hepatic function in a retrospective case series.

We performed a chart review of all patients treated simultaneously with MTX and INH at John H. Stroger Jr. Hospital of Cook County (Chicago, IL, USA). The primary endpoint was clinically relevant worsening in transaminase levels, which was defined as an elevation to at least 3 times the upper limit of normal (ULN). The ULN for alanine transferase (ALT) and aspartate transferase (AST) was 35 units/l and 40 units/l, respectively.

Between January 2001 and August 2008, 41 patients concomitantly received INH and MTX. Despite clinical followup of all patients, complete laboratory data were only available for the 40 patients who served as the primary cohort. Briefly, the majority of the patients were women: 34 (85%). Rheumatoid arthritis (RA) was the primary diagnosis in 37 patients (92.5%), psoriasis in 2 (5%), and spondyloarthritis in 1 (2.5%). The mean age was 49 \pm 12 years (range 27–77). The mean MTX dose was 17.3 \pm 6.9 mg/week (range 7.5–35). All patients received INH 300 mg with vitamin B6 50 mg. Average combined treatment with INH and MTX was 6.9 months (range 3–11). There was no evidence of hepatotoxicity, such as nausea, vomiting, abdominal pain, or jaundice. Similarly, review of all outpatient and hospital records yielded no evidence of any significant adverse events. There were no cases of transaminase elevation greater than 3 times the ULN at the time of INH discontinuation. The mean ALT and AST prior to INH therapy were 21 \pm 12.3 U/l and 21 \pm 8.5 U/l, respectively, and at the end of the INH regimen 24 \pm 17.5 U/l and 24 \pm 11.7 U/l, respectively. There was no significant change in transaminases between pre- and post-INH therapy ($p = 0.3$). Of the 35 patients with available interval transaminase values, 6 had elevations above ULN. The peak interval ALT in 6 patients were 46, 49, 51, 60, 62, and 106 U/l. The peak interval AST for 2 patients were 56 U/l and 112 U/l. As noted, 1 patient developed a peak ALT level that was greater than 3 times the ULN. In this case, the ALT reached 106 U/l, but improved spontaneously to 47 U/l. Neither INH nor MTX treatment was altered in these patients. Thirty-nine of 40 patients completed the planned INH regimen, and 1 patient was noncompliant after 3 months.

In our small study, the combination of 2 commonly used agents, INH and MTX, appeared to be safe despite the well recognized potential hepatotoxicity of each. Transient and spontaneously resolving low-level eleva-

tion of transaminases occurred in 6 patients (15% of the population), but did not require alteration in the dosing regimen of either medication. Our results are comparable to the finding by Mor, *et al*, who also reported safety of concomitant MTX and INH therapy on 44 patients with RA⁵. Another study reported different findings, with 50% of cases developing significant hepatotoxicity with combined administration of MTX and INH⁶. This study was severely limited by small sample size of 8 patients.

Our study has several limitations. First, as it was a retrospective study of a small cohort, it was not well powered to detect differences. Second, data on other potentially hepatotoxic medications were not collected during our chart review. Third, liver biopsies were not performed; hence, subclinical hepatotoxicity cannot be definitively excluded.

In this small retrospective cohort, INH was safely coadministered with MTX without evidence of significant or additive toxicity. No clinically significant sustained worsening of transaminase levels was observed.

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