Liver Function Tests During Tuberculosis Treatment and the Implications on Monitoring for Hepatotoxicity

Introduction and Objectives

Drug-induced hepatotoxicity is a common complication of tuberculosis treatment[1]. Guidelines based on expert opinion are available, but the natural history of liver enzyme measurements over the course of treatment and the most effective approach to monitoring on treatment remains unclear[2].

We investigated the pattern of liver enzyme levels in the REMoxTB trial to describe the magnitude and timing of elevations, along with factors that could influence enzyme patterns, and related this to liver function monitoring.

Methods

Patients received either standard tuberculosis treatment (2EHRZ/4HR), or a four-month regimen with moxifloxacin substituted for ethambutol (isoniazid arm, 2MHRZ/2MHR) or isoniazid (ethambutol arm, 2EMRZ/2MR). Liver function tests were performed at weeks 0, 2, 4, 8, 12, 17, and during adverse events. The Chi Square or Fisher's exact test was used for testing proportions among groups, log rank test for comparison of time, and Students t test for comparison of means.

Results

639 patients were allocated to receive standard therapy as controls, 654 to the isoniazid arm, and 635 to the ethambutol arm (see Table). 60 patients (9.4%) taking standard therapy developed a peak ALT/AST ≥3xULN at median time 28 days (IQR 14-56). The mean difference in time to reach peak ALT was 7 days between isoniazid-containing regimens and the ethambutol arm, and a higher proportion of Asian patients elevated ALT/AST ≥3xULN in isoniazid-containing arms (51.0% vs 26.3%, ($p<0.001$)). Of the 40/421 (9.5%) HIV positive in Africa, 24/421 elevated ALT/AST ≥3xULN compared to 25/121 (5.7% vs 20.7%, ($p<0.001$)) in India elevating ALT/AST ≥3xULN where 2/121 (1.7%) were HIV-positive.

Discussion

Monitoring liver function routinely for the first two months of HRZE therapy would have detected approximately 75% of patients with a peak enzyme elevation of ≥3xULN, and we would recommend this as a standard of care based on these results. However, there is reassurance that over 90% of patients completed therapy without an ALT/AST result ≥3xULN. HIV positive and Asian patients were at higher risk of liver enzyme elevation and there was a shorter time to peak ALT/AST for those receiving isoniazid.

		2EHRZ/4HR	2MHRZ/2MHR	2EMRZ/2MR	p value
ALT RESULT	**n◊**	634	649	634	***
	Median peak value as xULN (IQR)	0.83 (0.56-1.35)	0.78 (0.53-1.23)	0.73 (0.51-1.09)	0.046† 0.000‡
	Median time to peak value in arm (days)	28 (14-84)	28 (14-84)	55 (14-84)	0.972† 0.017‡
	No with peak ≥3xULN (%)	41 (6.5%)	35 (5.4%)	25 (3.9%)	0.130
	No with peak ≥5xULN (%)	20 (3.2%)	18 (2.8%)	14 (2.2%)	0.580
	No with peak ≥10xULN (%)	7 (1.1%)	2 (0.3%)	3 (0.5%)	0.204§
AST RESULT	**n**	639	654	635	
	Median peak value as xULN (IQR)	1.02 (0.73-1.48)	0.93 (0.68-1.45)	0.90 (0.68-1.28)	0.026† 0.000‡
	Median time to peak value in arm (days)	52 (14-84)	28 (14-84)	55 (13-84)	0.160† 0.917‡
	No with peak ≥3xULN	46 (7.2%)	41 (6.3%)	27 (4.3%)	0.074
	No with peak ≥5xULN	21 (3.3%)	17 (2.6%)	12 (1.9%)	0.292
	No with peak ≥10xULN (%)	8 (1.3%)	5 (0.8%)	5 (0.8%)	0.668§
	No of liver-related withdrawals	11 (1.7%)	7 (1.1%)	4 (0.6%)	0.178

◊Some patients not included due to missing ALT results

† Isoniazid arm against standard therapy

‡ Ethambutol arm against standard therapy

§ Fisher's exact test

References

1) Thompson N, Caplin M, Hamilton M, et al, Anti-tuberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995;8:1384-1388
2) Ormerod P, Campbell I, Novelli V, et al. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998;53:536-548
3) Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. *Am J Respir Crit Care Med* 2006;174:935-952
4) Tostmann A, Boeree MJ, Aarnoutse RE, et al. Anti-tuberculosis drug-induced hepatotoxicity: Concise up-to-date review. *J Gastroenterol Hepatol* 2008;23:192-202.
5) Singanayagam A, Sridhar S, Dhariwal J, et al. A Comparison Between Two Strategies for Monitoring Hepatic Function During Antituberculosis Therapy. *Am J Respir Crit Care Med* 2012;185:653-659