MONITORING FOR HEPATOTOXICITY DURING ANTITUBERCULOSIS TREATMENT

GENERAL RECOMMENDATIONS

A consensus statement of
the Tuberculosis Control Coordinating Committee of
the Hong Kong Department of Health and
the Tuberculosis Subcommittee of
the Coordinating Committee in Internal Medicine of
the Hospital Authority, Hong Kong

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Background

Treatment of tuberculosis (TB) involves several drugs in combination for six or more months. An updated set of guidelines has been published by a working group of the Tuberculosis Control Coordinating Committee/ Tuberculosis & Chest Subcommittee of the Department of Health and the Hospital Authority (TBCCC/TBSC).[1] In view of the concern about the risk of hepatotoxicity, this short paper has been prepared to address the issue in greater depth.

Many of the commonly used anti-TB drugs are associated with significant potential of causing hepatotoxicity. While the occurrence of drug-induced hepatitis is difficult to predict, it has been observed that certain patients are at higher risk of developing drug-induced hepatitis during the course of anti-TB chemotherapy. These include patients with pre-existing liver diseases, particularly those associated with chronic viral infection due to Hepatitis B, Hepatitis C, and HIV, the alcoholics, the elderly and the malnourished.[2-4]

The exact role of regular monitoring of liver function tests in patients receiving antituberculosis drugs remains controversial. Certain guidelines only emphasize the need of clinical monitoring without mentioning regular biochemical monitoring,[5,6] while a number of authorities recommend routine biochemical monitoring among the high risk groups.[7-9]

Transient changes in alanine transaminase and bilirubin levels are relatively common during antituberculosis chemotherapy and do not signify true hepatotoxicity. However, progressive rise in alanine transaminase and bilirubin levels is much more ominous. Existing data do not allow reliable prediction of the exact clinical course of asymptomatic patients with moderate degree of biochemical derangement. Opinions therefore differ as at what cut-off level of liver dysfunction should modification of treatment regimen be initiated. For the alanine transaminase level, some recommend stopping the hepatotoxic drugs three times or above that of normal,[8-12] while others recommend five times.[6,7,13] The recommendations regarding the level of bilirubin are also not uniform.[13]

Furthermore, opinions on the frequency and duration of biochemical monitoring also differ. While more frequent testing may be more likely to pick up those cases with rapid progression, cost-effectiveness and patient acceptance are practical issues among those without clinical symptoms. Whether monitoring should be performed throughout the whole course of anti-TB treatment, or just during the initial treatment phase also requires deliberation.

More recently, a number of fatal cases of drug-induced hepatitis have been reported during the course of treatment of latent TB infection (LTBI) since the publication of the guidelines for the treatment of LTBI by ATS/CDC.[14] Although the

absence of data on the denominator precludes an accurate assessment of the risk, an updated statement has been promulgated recommending more vigilant measures in liver function and clinical monitoring.[13]

A recent study in Hong Kong showed that among patients treated with anti-TB drugs, the incidences of liver dysfunction and symptomatic hepatitis were rather high among Hepatitis B carriers compared with non-carriers[2] (Table 1). Another local study also quoted a significant rate at 12% of clinically symptomatic hepatic dysfunction among 1,181 hospital patients who received rifampicin, isoniazid with or without pyrazinamide and other drugs.[15] Although the definitions employed for those hepatitic reactions are not exactly similar, the rates of liver dysfunction found in these local studies are clearly higher than those reported elsewhere.[16,17]

Recommendations

Basing on the available clinical information, international guidelines, and experiences from local experts, a consensus statement has been prepared by a working group of the TBCCC/TBSC on clinical and biochemical monitoring of hepatotoxicity during anti-TB treatment in the local setting:

(a) For all patients undergoing treatment with potentially hepatotoxic anti-TB drugs, health education should be provided to alert them of the symptoms suggestive of hepatitis, which include loss of appetite, nausea, vomiting, fever, and jaundice. They should be advised to report such symptoms promptly to the nursing or medical staff should these arise.

(b) During medical consultations in the course of anti-TB treatment, all patients should be assessed clinically for symptoms and signs suggestive of hepatitis.

(c) Directly observed treatment (DOT), apart from ensuring treatment adherence, also allows health care workers to monitor the patients closely for such symptoms and signs.

(d) Patients developing symptoms suspicious of hepatitis should have liver function tests checked, and in the case of clinical suspicion of significant hepatitic reactions, the anti-TB drugs may have to be stopped even before the availability of the test results.

(e) Patients at risk of developing drug-induced hepatitis should be identified at the beginning of the treatment course. Patients with pre-existing liver diseases, the alcoholics, the elderly and the malnourished constitute the most clearly defined risk groups. Liver function tests should therefore be checked before the start of anti-TB treatment.

(f) For those who belong to the risk groups as mentioned in (e), it would be desirable to monitor liver function tests once every two weeks during the initial two months of treatment, or more frequently as clinically indicated.

(g) In view of the high Hepatitis B carrier rate and the high incidence of drug-induced hepatic dysfunction among them locally, it is also desirable to check the HBsAg status of patients who need to receive anti-TB treatment. Close clinical and biochemical monitoring should also be considered for hepatitis B carriers as in (f).

(h) Regarding the cut-off levels of liver dysfunction for withholding potentially hepatotoxic anti-TB drugs in patients without symptoms, the followings are recommended:
   (i) Alanine transaminase level rising to three times or above the upper limit of normal;
   (ii) Bilirubin level rising to two times or above the upper limit of normal.

Discussion and conclusions

Biochemical monitoring is not a replacement for close clinical monitoring. Clinical heterogeneity dictates that each case should be assessed individually with the monitoring procedures tailored accordingly. More frequent and intensive biochemical monitoring may be indicated in situations where the patient's condition or the liver enzyme levels change rapidly. If the anti-TB drugs are given for the treatment of latent TB infection, the standard for safety monitoring is clearly higher than that for the treatment of active disease.[18]

Not uncommonly, mildly elevated pretreatment liver enzymes are encountered among TB patients without any other evidence of liver disease. When these patients are given the full treatment regimen,[1] their enzyme levels are often observed to revert to normal and this phenomenon is presumably related to the

resolution of hepatic TB microgranulomas. However, for those patients with evidence of underlying chronic liver diseases, anti-TB drugs should be started carefully. Depending on the nature of the underlying liver problem, it may be necessary to begin with a potentially less hepatotoxic combination of drugs, and then modify the regimen according to tolerance.

If significant drug-induced hepatitis develops, careful balance of all factors is required to decide on when and how to resume treatment. In case of doubt, experts in the field should be consulted. It should be noted that patients with active TB disease would develop detrimental consequences if the TB is left untreated, particularly if the disease is extensive. Hence, the decision on when to resume treatment with anti-TB drugs should be made not only by the time the liver function tests reverting to the normal or pretreatment level, but also on the rate of TB disease progression and the disease severity. Sometimes, a regimen with less hepatotoxic drugs or a combination of drugs without potential hepatotoxicity may have to be tried first, with the more potent but potentially hepatotoxic drugs added subsequently one after the other (Table 2). It is generally desirable to include both isoniazid and rifampicin in the final regimen whenever possible, so that the duration of treatment does not need to be excessively prolonged. During resumption of the treatment, the liver chemistry should be closely monitored, and the frequency of monitoring usually depends on the severity of the liver dysfunction that has had occurred and the drugs on trial. It has to be noted that the cause of that hepatitis, apart from being drug-induced, could be due to alternatives such as viral infections, or induction by other drugs used at the same time. Resumption of treatment utilizing the original full drug regimen may rarely be possible.

Although there has been substantial progress in the treatment of certain liver diseases, like chronic viral hepatitis, the implications of these advances on the treatment of tuberculosis have not yet been fully clarified. The above guidelines and recommendations need to be reviewed periodically with the availability of future updates in scientific data and medical literature, as well as further accumulation of local experience.

Table 1. Rate of liver dysfunction and symptomatic hepatitis among patients given anti-TB drugs, among HBV carriers as compared with non-carriers, and among HBV carriers not given anti-TB drugs[2]

	HBV carriers given anti-TB drugs	Non-carriers given anti-TB drugs	HBV carriers not given anti-TB drugs
Total number	43	276	86
Liver dysfunction *	15 (34.9%)	26 (9.4%)	7 (8.1%)
Symptomatic hepatitis #	7 (16.3%)	13 (4.7%)	1 (1.2%)

* *Liver dysfunction is defined as an increase in ALT levels to 1.5 times above the upper limit of normal on at least 2 consecutive occasions within 4 weeks. For patients with increased pretreatment ALT, the elevation in ALT had to be greater than 1.5 times the baseline level.*

\# *Symptomatic hepatitis is defined as the presence of malaise, nausea, vomiting, lethargy and/or right upper quadrant discomfort together with the presence of liver dysfunction irrespective of the severity of the biochemical abnormality.*

Table 2. Anti-TB drugs and potential for hepatotoxicity

Potentially hepatotoxic drugs	Drugs with much lower or little potential for hepatotoxicity
Isoniazid Rifampicin, Rifabutin Pyrazinamide Ethionamide, Prothionamide Para-aminosalicylic acid	Streptomycin, Kanamycin, Amikacin, Capreomycin Ethambutol Ofloxacin, Levofloxacin, Ciprofloxacin Cycloserine

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