Management of anti TB drug induced hepatitis

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Anti TB drug induced hepatitis (AIH) is one of the complications encountered in the treatment of tuberculosis. While studies in USA and UK have reported a 3% and 4% incidence of AIH respectively with rifampicin/isoniazid (with or without pyrazinamide in UK)[1,2], studies from India have reported incidence ranging from 2% to as high as 30%[3,4,5]. Pooled data from four prospective Indian studies have shown that the risk of hepatitis to be 11.5% whereas meta analysis of 14 studies from the west found the risk to be 4.28%[6]. A recent study done in Sri Lanka showed an incidence of 9% in the study population [senaratne et al. in press]. Many risk factors for AIH have been described. They include advanced age, high alcohol consumption, extensive disease, hypoalbuminaemia, slow acetylator phenotype, female sex and endemic viral hepatitis[6,7,8]. Of these, age and severe disease have featured as risk factors for AIH in most studies. AIH occurs most commonly during the first few weeks of treatment[9,10]. In a study population of Sri Lankan patients, out of those who developed AIH 98.6% did so during the first eight weeks of treatment (senaratne et al, inpress). Of the essential anti TB drugs, namely rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin, it is the former three which cause liver injury. Isoniazid and pyrazinamide are responsible for hepatocellular damage while rifampicin can cause a pure hyperbilirubinaemia by interfering with hepatic uptake and excretion of bilirubin.

Transaminases rise during first 2-3 weeks of ATT (anti-tuberculous treatment). Levels do not go beyond 2 to 3 folds of the upper limit of normal (ULN) and come down despite continuation of treatment. Serum bilirubin (SB) and transaminases should be measured on all patients prior to treatment. Baseline levels will reveal any pre-treatment abnormality which can be due to TB itself or other reasons. In a patient whose baseline SB and alanine transferase (ALT) are normal, they need to be repeated only if the patient complains of symptoms such as deterioration of appetite, nausea, vomiting, deterioration of general condition, fever, malaise or is found to be icteric. SB and ALT should be repeated weekly for two weeks and every two weeks thereafter for two months in patients whose baseline levels are high or in those with chronic liver disease, eg:- heavy alcohol consumption, chronic active hepatitis cirrhosis and those known to have hepatitis B or C antigen positive.

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Diagnosis

Patients should be informed about the adverse reactions to anti TB drugs, some of which are minor and can be ignored while the others such as hepato-toxicity are serious and should be managed appropriately. They should be given clear instructions to stop treatment and report to the clinic if they develop deterioration of appetite with nausea and/or vomiting. Diagnosis of AIH is based on symptoms of hepatitis with elevation of either transaminases or SB or both. However, there is no consensus on the level of transaminases and SB beyond which the diagnosis of AIH is made. WHO guidelines merely advise to stop ATT when the diagnosis of AIH is made but does not elaborate on transaminase and bilirubin levels[11]. Mitchell et al recommend that rifampicin and isoniazid should be stopped if the level of hepatic transaminases rise to three times the normal value or serum bilirubin rise[12]. On the other hand the Joint Tuberculosis Committee of the British Thoracic Society recommends that treatment should be stopped when transaminase levels rise to five times the normal or SB rises[10], while Dossing et al suggest that treatment should be stopped when transaminases rise more than six times the ULN with symptoms or SB rise to twice the ULN and that one can continue treatment until transaminases rise to 8 times the ULN if the patient is asymptomatic[7]. Our experience is that Sri Lankan patients develop symptoms when ALT rises more than 3 times the ULN or SB rises above normal. Therefore we suggest that the diagnosis of AIH is made when a patient on ATT develops symptoms of hepatitis with either ALT rising above three times the ULN or SB level rising above normal or both [Senaratne et al in press]. It is important to keep in mind that derangement in liver functions in a patient who is on ATT may not necessarily be due to anti tuberculosis drugs although it is the most likely cause. Other causes such as viral hepatitis have to be considered especially when the elevation of transaminases is very high with patient having constitutional symptoms such as fever.

Management

If the patient is not so unwell and especially in the case of non infectious tuberculosis, treatment is stopped until liver functions return to normal. If it is not possible to stop treatment as in the case of sputum positive pulmonary TB, very ill patients, extensive pulmonary involvement and miliary TB, one of the following alternatives can be adapted.

a). Continue streptomycin and ethambutol until liver functions return to normal. This is a weak regimen as it is only streptomycin which is bactericidal while ethambutol is bacteriostatic. Furthermore, in case the organisms are resistant to one drug, it amounts to monotherapy with the other. Therefore, addition of a bactericidal secondline drug , namely a quinalone (ciprofloxacin or ofloxacin) strengthens the streptomycin and ethambutol combination.

b). A cobmination of streptomycin, isoniazid and ethambutol can be given to patients whose liver function test profile shows elevated SB with normal transaminases. Such a LFT profile is due to rifampicin, which interfere with uptake of bilirubin by the liver.

Once liver functions return to normal isoniazid, (H) rifampicin (R) and pyrazinamide (Z) should be rentroduced sequentially (in that order) each drug starting with a lower dose. It is recommended to introduce H first with 50mg on day 1 and increasing to 300mg over 3-4 days. If there is no reaction, add R starting with 75mg on the first day and increase to full dose over 3-4 days. If the patient is asymptomatic and liver functions remain normal, this should be followed by Z starting with 250mg increasing to full dose over 3-4 days. Re introduction of drugs should be closely monitored by assessment of ALT and SB. In the case of patients who are taken off all anti TB drugs, re introduction is best done under the cover of streptomycin and ethambutol to avoid the emergence of drug resistance.

Standard treatment can be re-instituted in most patients. Once it is done, alternative drugs added temporarily can be withdrawn. Failure to re-institute standard drug regimen necessitates altering treatment regimen which is best done in consultation with a specialist in the field with experience.

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