ATT- A Double Edged Sword?

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Gude and Bansal: ATT Induced Acute Liver Failure

Antitubercular therapy (ATT) induced hepatotoxicity, although well known to clinicians, is often over looked and underrated. Given the low threshold of starting ATT, especially empirically, the adverse manifestations can take a considerable toll. A variety of associated risk factors compound the morbidity. We throw light on one such a case where ATT was detrimental to the patient and review the literature and possible preventive strategies.

Key words: Acute liver failure, antitubercular therapy, hepatotoxicity

We would like to share our experience about a patient on ATT that proved fatal. A 52 year old male, an occasional alcoholic and smoker, with a history of starting ATT (isoniazid-300 mg, rifampin-450 mg, ethambutol-800 mg, pyrazinamide 1500 mg per day for one month) for pulmonary tuberculosis, presented with altered sensorium from one day preceded by jaundice for 5 days. On examination there was icterus, BP-100/60 mm Hg, abdomen soft, with no palpable masses and he was moving all limbs. Labs showed Hb-9.8 g/dl, total WBC-9200, ESR-8 mm 1st h, serum creatinine-1.14 mg/dl, Prothrombin-130.3 s, INR (International Normalized Ratio)-10.4, total bilirubin-17.3 mg/dl, direct bilirubin-9.2 mg/dl, ALT-4260 IU/L, AST-3090 IU/l, (gamma glutamyl transferase) GGT-39 U/l, albumin-2.2 g/dl, venous ammonia-47.5 µmol/l. CT brain showed mild cerebral edema. Ultrasonography showed normal liver span but altered echo-texture and minimal ascites. Provisionally diagnosed of fulminant hepatic failure (Acute liver failure-ALF) with Grade III encephalopathy, and given his unaffordability for orthotopic liver transplantation (meets King's college criteria), supportive therapy with vitamin-K, albumin, fresh frozen plasma (FFP), dextrose, rifaximin, L-ornithine-L-aspartate and lactulose was started. Over the next few days he developed respiratory failure, cardiac arrest and died.

Three rare cases of tuberculosis per se causing ALF have been described with hyponatremia and hepatomegaly as the features at presentation[1]. Usually widespread miliary tuberculosis (TB) underlies such cases although our case did not qualify for military TB owing to features like organ systems other than lung being spared, low ESR and the temporal association with ATT.

Drug-induced liver injury (DILI) accounts for 7% of adverse effects, 2% of jaundice in hospitals, and about 30% of fulminant liver failure[2]. A variety of drugs have been incriminated in drug induced ALF apart from ATT like paracetamol, lamotrigine, nimesulide, carbamazepine, levetiracetam, clarithromycin, azithromycin, minocycline, ecstasy etc[3,4]. Though in the west paracetamol toxicity is the leading cause of ALF (39% of the cases in USA[5], 73% in UK[6]), ATT associated ALF is the commonest drug-induced ALF in South Asia[7]. ATT can be a cause of hepatotoxicity in 5% and is fatal in up to 0.2% of patients[8].

The WHO classification graded the hepatotoxicity by liver enzyme level proposing Grade I –for AST 51-125 U/l, Grade II for -AST 126-250 U/l, Grade III for-AST 251-500 U/l, and Grade IV for AST >500 U/l or >250 U/l with symptoms of fulminant hepatitis[9]. Hy's law states that jaundice preceded by markedly elevated transaminases point to severe liver disease with a 10% possibility of ALF.[10] Our patient with Grade IV hepatotoxicity, was thus at utmost risk.

The hepatotoxicity of isoniazid (H) is mainly from the diminished glutathione-related thiols and antioxidant glutathione peroxidase and catalase

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activities owing to the reactive metabolites of mono-acetyl hydrazine (MAH). Covalent binding of MAH to liver macromolecules, enhanced cytochrome P450 2E1 activity and other metabolic idiosyncratic mechanisms also seem to play a role. Pyrazinamide (Z) exhibits both dose-dependent and idiosyncratic hepatotoxicity sporting eosinophilia and liver injury or granulomatous hepatitis. Pyrazinamide alters nicotinamide acetyl dehydrogenase levels resulting in generation of free radical species. Similarity in molecular structure may explain shared mechanisms of injury for H and Z. Rifampin's (R) adverse effects appear to be via inhibition of the major bile salt exporter pump, dose-dependent competition and impeded secretion of bilirubin and hypersensitivity reactions. Lipid peroxidation, major histocompatibility complex class II associated HLA-DQ alleles and choline deficiency leading to lowering of phospholipids protein synthesis with alteration in cell wall configuration also seem to play a role in the H-R mediated hepatotoxicity[2,11].

The hypersensitivity reactions from these drugs are mediated through the haptens or neoantigens formed by the immunogenic drug or its metabolites that may be free or covalently bound to hepatic proteins. These antigens may evoke antibody-dependent cytotoxic, T-cell, and occasionally eosinophilic hypersensitivity responses. Tumor necrosis factor, interleukin (IL)-12, and IFN-γ released as a result, promote apoptosis[12].

A study spanning 23 years on 1223 consecutive ALF patients showed that ATT alone was the cause in 5.7% of ATT-ALF patients with a mortality rate of 67.1%[12]. The median icterus to encephalopathy interval was 4.5 days (5 days in our case) and the median duration of ATT before ALF was 30 days with advanced encephalopathy at presentation in 76% (both seen in our case). Bilirubin ≥10.8 mg/dl, prothrombin time ≥26 s, and grade III/IV encephalopathy at presentation independently predicted mortality. Advancing age (>65), female gender, poor nutritional status and presence of cerebral edema amplify the risk associated with hepatotoxicity. ATT was prescribed empirically without definitive evidence of tuberculosis in 62.8% patients which points toward the possible disastrous outcomes in indiscriminate use.

In another study discerning ATT-induced hepato-toxicity, jaundice was the presenting symptom in 61% while prodromal symptoms were seen in 39%[13]. The mean duration of treatment before the onset of hepatitis was significantly longer in the fatal group than the rest. In 93% of them reintroduction of isoniazid and rifampicin was possible after resolution of ATT-induced hepatitis. A study evaluated the effect of reintroduction of 3 different regimen of ATT (HRZ, ATS guideline therapy and British Thoracic Society guideline therapy) on 175 patients with a diagnosis of ATT Drug Induced Hepatotoxicity (DIH)[14]. Only 10.9% had recurrence of DIH during follow-up and it didn't differ among the groups. Pretreatment serum albumin level was a statistically significant predictor of future recurrence of DIH on reintroduction of antituberculosis drugs. This study underscores that in settings of life threatening tuberculosis or bilateral extensive pulmonary tuberculosis, all three of these drugs may be reintroduced simultaneously at full dosage safely after desensitization with adequate surveillance. Co-infection with HBV in those on anti-TB medicines makes the condition more critical and they are noted to have a higher incidence of liver damage with an earlier onset and even worse degree of damage to the liver[15].

Using injectable poly DL-lactide-coglycolide microparticles, and lipid based inhalable sustained-drug-delivery as vehicles for administering ATT may lower the risk of hepatotoxicity[16]. Curcumin is shown to suppress production of superoxide by macrophages, exert potent anti-inflammatory action that inhibits production of TNF-α, interleukin (IL) 1-β and the activation of NF-κB. Apart from demonstrating strong antioxidant properties, it inhibits lipid peroxidation in liver microsomes, erythrocyte membranes and brain homogenates (by maintaining a higher level activity of SOD, catalase and glutathione peroxidase). *Tinospora cordifolia* induces enzymes of drug metabolism, inhibits lipid peroxidation and bolsters the antioxidant system (via enhanced cytochrome P450, NADP-cytochrome (P sub 450) reductase, glutathione-s-transferase, DT diaphorase, SOD and catalase). It has shown to improve liver function, protect against toxic assaults and increase protein synthesis by liver. It also has immunostimulant properties enhancing cell mediated as well as humoral immune response. Together, *Curcuma longa* and *Tinospora cordifolia* have shown excellent hepatoprotective potential and are proved beneficial in ATT-induced hepatotoxicity[8,17]. The

synergistic combination of *Tinospora cordifolia* and *Phyllanthus emblica* also significantly prevented hepatic necrosis in ATT-ALF[18]. A polyherbal preparation (Livina-2 capsules twice daily) given with ATT drugs, markedly attenuated liver dysfunction as shown by the significantly lower transaminasemia compared to placebo and ATT alone[19]. silymarin and tiopronin have showed hepatoprotective effects in ATT induced ALF[20].

MRI findings of ALF patients reinforced the occurrence of cytotoxic cell swelling as they had significantly lower apparent diffusion coefficient in all cortical and deep white and gray matter regions compared to controls[21].

Patient education about the symptoms of hepatitis and its prompt recognition, early evaluation with close clinical monitoring and regular follow up are some of the key components of preventing ATT-hepatotoxicity. Proper counseling and reinforcement of the benefits of treatment and adherence to the prescribed drug regimen can be observed in such keen follow up. Baseline and monthly (or biweekly) testing of liver enzymes especially in high risk groups like chronic ethanolics, HIV, pregnancy and within 3 months after delivery, chronic liver disease, or usage of concomitant hepatotoxic medications certainly helps one gauge the degree of ATT-hepatotoxicity. Transaminasemia higher than three times the upper limit of normal in a symptomatic patient or five times the upper limit of normal in the absence of symptoms should raise the antennas of clinicians and cessation of the offending drugs should be seriously considered.

We attempt to highlight the ubiquitous indiscriminate prescription of ATT with poor surveillance of adverse effects and the resulting dire catastrophes and call for emergent attention on the same.

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