

## ATT-induced Hepatotoxicity: Culprit Drug

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Sir,

Tuberculosis is an ancient disease, a major global health problem and a leading cause of death, especially among economically productive age group. India accounts for the highest tuberculosis burden i.e. approximately 20% of the total global burden. According to the WHO Global report 2015, TB remains one of the deadliest communicable disease.<sup>1</sup> Physical and social factor plays important role among patients taking treatment for tuberculosis.<sup>2</sup> The outcomes of various anti tubercular therapies (ATT) varies from place to place, as Fotso stated that health outcomes are worst in slums than in urban areas or even rural areas.<sup>3</sup> Emergence of anti- tubercular drug resistance due to non- compliance has further aggravated the public health problem.

Tuberculosis is a mycobacterial disease, treatable with anti tubercular therapy (ATT), commonly used drugs are, Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as first line drugs.<sup>4</sup> All these drugs are used in combination for few months (2 to 6 months). Common side / toxic effects of these drugs are; Isoniazid causes peripheral neuropathy and hepatotoxicity (elevated serum transaminases and serum bilirubin); Rifampicin causes immune-allergic reactions and hepatotoxicity (elevated serum transaminases, alkaline phosphates and serum bilirubin); Pyrazinamide causes joint pains (increased serum uric acid) and hepatotoxicity (elevated serum transaminases and serum bilirubin).<sup>5</sup>

These three drugs isoniazid, rifampicin and pyrazinamide are hepatotoxic and this toxicity manifests in the form of nausea, vomiting, weakness, tiredness and yellowish discoloration of eyes. These side effects can be due to one/ two or all of the three drugs and some of the patients are not able to tolerate these and as a result stop taking anti tubercular drugs.

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Management of these side / toxic effects are by stopping all the 3 drugs till the patient become asymptomatic with symptomatic treatment and till his Liver function test (LFT) are within normal range. As for as the individual drug is concerned, it has been observed clinically that if symptoms of hepatotoxicity appears within first 10 days of initiation of ATT rifampicin is culprit, if symptoms arise after by the end of second week of initiation of ATT, there are more chances of isoniazid being the culprit and if the symptoms arise after three weeks most liable drug is pyrazinamide. Sometimes one, two or all the three drugs are responsible. These side effects are more common in alcoholics.

As soon as the patient is asymptomatic and LFT are within normal range, the drugs one by one should be restarted in small doses and gradually the dose should be increased till therapeutic dose is achieved and should withdraw immediately if there is any indication of recurrent liver involvement. Isoniazid is to be first reinitiated followed by rifampicin and then pyrazinamide. Generally patient takes 1 to 2 weeks to tolerate one drug and after 2 weeks another drug is added and generally after 4 weeks third drug is added.

Monitoring the degree of ATT induced hepatic injury is difficult in these patients as fluctuations in the biochemical indicators of LFT relating to pre-existing disease act as confounding factor. Therefore sometime it is difficult to decide whether the derangement in LFT is due to ATT or is manifestations of already existing liver diseases. However to exclude this pre-existing

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Due to long duration of therapy concurrent use of multiple drugs, adverse effects are most important clinical consideration in patient taking ATT. Hepatotoxicity is most serious one which not only leads to high morbidity and mortality, but also decreases anti TB treatment effectiveness, owing to non adherence and leading to multi drug resistance tuberculosis (MDR TB), therefore regular LFT monitoring is required.

## References

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