

Is it safe to double the dose of rifampicin to shorten tuberculosis treatment duration?

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Background

The current 6-month TB treatment regimen is still too long. Use of higher doses of rifampicin(R) might ensure faster lung sterilization with subsequent reduction in treatment duration. However, R can induce liver toxicity and safety data using high dose rifampicin are lacking. We assessed whether increasing the dose of rifampicin (R) from 10 mg/kg to 15 or 20 mg/kg, results in an increase in grade 3 or 4 hepatic adverse events and/or serious adverse events (SAE).

Methods

In a Phase IIB, open-label randomized controlled trial in Bolivia, Peru, and Uganda, 300 HIV negative patients with newly diagnosed, smear positive, drug susceptible pulmonary tuberculosis were randomly assigned to one of three regimens containing ethambutol, isoniazid, rifampicin, and pyrazinamide daily for 8 weeks followed by isoniazid and rifampicin daily for 18 weeks. The regimens differed only by the R dose during the first 16 weeks: 1 control regimen with R at 10mg/Kg and 2 study regimens with R at 15mg/Kg (R15) and 20mg/Kg (R20). Serum alanine transferase (ALT) measurements were carried out at regular intervals. Eight week culture conversion was used as surrogate marker for treatment efficacy.

Results

There were 7 grade 3 increases in ALT levels, 1/100 (1.0%) in R10, 2/100 (2.0%) in R15 and 4/100 (4.0%) in R20 regimens respectively (trend test $p=0.15$). R was discontinued due to liver toxicity in 1 patient (R15). There were no grade 4 ALT increases. There was a non-significant increase in culture conversion rate with increasing rifampicin dosage, 75% (69/92) R10, 82.5% (66/80) R15, and 83.1% (76/91) R20, ($p=0.16$).

Conclusions

There was no significant increase in liver toxicity when rifampicin dose increased from 10mg/kg to 15mg/kg or 20mg/kg.

The use of high-dose rifampicin in shortening of TB treatment duration from 6 months to 3 or 4 months can be possible if its safety is assured. Results of RIFATOX trial, show no significant increase in drug-induced Liver toxicity even with doubling of the normal dose of rifampicin.