INT J TUBERC LUNG DIS 19(7):805–807

http://dx.doi.org/10.5588/ijtld.14.0702

RMP exposure is lower in HIV-infected TB patients receiving intermittent than daily anti-tuberculosis treatment

A. K. Hemanth Kumar,* G. Narendran,* R. S. Kumar,* G. Ramachandran,* L. Sekar,* K. Raja,† S. Swaminathan*

***National Institute for Research in Tuberculosis, Chennai, †Government Hospital of Thoracic Medicine, Chennai, India**

SUMMARY

We compared the pharmacokinetics of rifampicin (RMP) during daily and intermittent (thrice weekly) anti-tuberculosis treatment in human immunodeficiency virus infected tuberculosis patients. Patients treated with a thrice-weekly regimen had significantly lower plasma peak concentration, area under the time concentration curve from 0 to 24 h and higher oral clearance of RMP than those treated with the daily regimen. The median values were respectively 3.7 and 6.4 μg/ml ($P < 0.001$), 20.7 and 29.4 μg/ml.h ($P = 0.03$) and 21.7 and 15.3 ml/min ($P = 0.03$).

KEY WORDS: human immunodeficiency virus; tuberculosis; anti-tuberculosis treatment; pharmacokinetics; rifampicin

THE MANAGEMENT of tuberculosis (TB) in human immunodeficiency virus (HIV) co-infected persons poses multiple challenges. The duration and schedule of the administration of anti-tuberculosis drugs have remained major research issues in HIV-infected TB patients, as supporting evidence from randomised trials comparing the different anti-tuberculosis treatment regimens is lacking.

Rifampicin (RMP), an exposure or concentration-dependent killer of *Mycobacterium tuberculosis*, is an integral component of first-line anti-tuberculosis treatment. The emergence of acquired RMP resistance among treatment failure patients with HIV infection remains a matter of serious concern.[1,2] Advanced HIV disease with associated malabsorption causing low RMP concentrations could be an important risk factor for acquired RMP resistance.[3,4] We compared the pharmacokinetics of RMP during daily and intermittent (thrice weekly) anti-tuberculosis treatment in HIV-infected TB patients to evaluate differences caused by the drug administration schedule.

METHODS

Patients

A subpopulation of HIV-infected TB patients enrolled in a prospective, open-labelled, parallel arm, randomised controlled clinical trial (CTRI No. 476/09, NCT0933790) formed the study cohort. Patients aged >18 years with newly diagnosed smear- or rapid culture-confirmed pulmonary TB attending the clinics of the National Institute for Research in Tuberculosis in Chennai and Madurai, India, were recruited.

The clinical trial and the nested pharmacokinetic study were individually approved by the institutional ethics committees of the National Institute for Research in Tuberculosis, Chennai, the Government Hospital of Thoracic Medicine, Chennai, and Government Rajaji Hospital, Madurai, India.

Treatment

Eligible patients were randomised to receive a daily (2EHRZ+4HR), a part-daily (2EHRZ+$4H_3R_3$) or an intermittent anti-tuberculosis treatment regimen ($2E_3H_3R_3Z_3+4H_3R_3$).* The doses of the drugs in the daily and intermittent regimens were respectively RMP 450 mg (600 mg for those with body weight >60 kg), INH 300/600 mg, EMB 800/1200 mg and PZA 1500 mg. All patients were referred to the nearest antiretroviral treatment (ART) centre for ART initiation within 2–8 weeks of starting anti-tuberculosis treatment. Each dose of anti-tuberculosis treatment was directly supervised (directly observed

* E, EMB = ethambutol; H, INH = isoniazid; R, RMP = rifampicin; Z, PZA = pyrazinamide. Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the number of times the drug is taken each week.

Correspondence to: Soumya Swaminathan, National Institute for Research in Tuberculosis, Mayor V R Ramanathan Road, Chetpet, Chennai 600 031, India. Tel: (+91) 44 2836 9600. Fax: (+91) 44 2836 2528. e-mail doctorsoumya@yahoo.com; soumyas@nirt.res.in

Article submitted 17 September 2014. Final version accepted 5 March 2015.

Table Patient demographics and RMP pharmacokinetics in the daily ($n = 26$) and intermittent ($n = 15$) treatment groups

Variables	Daily treatment ($n = 26$) Median [IQR]	Thrice-weekly treatment ($n = 15$) Median [IQR]	*P* value
Age, years	35 [31.5–40.5]	39 [31–42]	NS
Body weight, kg	45 [38–48.5]	50 [39–55]	NS
Males, *n*	22	14	NS
RMP dose, mg/kg	9.9 [9.1–11.7]	9.8 [8.2–11.6]	NS
CD4 cell count, cells/mm^3	240 [16–877]	177 [45–899]	NS
C_{max}, μg/ml	6.4 [5.6–7.6]	3.7 [2.1–4.6]	<0.001
T_{max}, h	4.0 [2.0–4.0]	2.0 [2.0–4.0]	0.047
$AUC_{0–24}$, μg/ml.h	29.4 [20.6–41.0]	20.7 [14.3–29.3]	0.03
Cl, ml/min	15.3 [11.0–21.9]	21.7 [15.3–31.4]	0.03
$t_{1/2}$, h	2.2 [2.1–2.3]	2.6 [2.4–2.8]	<0.001

RMP = rifampicin; IQR = interquartile range; NS = non-significant; C_{max} = peak concentration; T_{max} = time at which C_{max} is attained; $AUC_{0–24}$ = exposure; Cl = clearance; $t_{1/2}$ = half-life.

therapy [DOT]) during intermittent treatment and 5 days a week during daily treatment.

Pharmacokinetic study

The pharmacokinetic study was undertaken after overnight fasting during the intensive phase of anti-tuberculosis treatment after a minimum of six doses. Serial blood samples (2 ml) were collected pre-dosing and at 1, 2, 4, 6, 8, 12 and 24 h after drug administration. Plasma RMP was determined using high-performance liquid chromatography.[5] The accuracy and precision of the method were respectively 102% and 95%. Peak concentration (C_{max}), time to attain C_{max} (T_{max}), area under the time concentration curve from 0 to 24 h ($AUC_{0–24}$), apparent oral clearance (Cl) and terminal elimination half-life ($t_{1/2}$) were calculated using the non-compartmental method.

Statistical analysis

Data analyses were performed using SPSS, version 14 (Statistical Package for the Social Sciences, Chicago, IL, USA). Differences in the pharmacokinetic parameters of RMP between the daily and intermittent regimens were studied using the Mann-Whitney test. The proportions were compared using the χ^2 test. $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Of the 41 patients who took part in the study, respectively 19, 15 and 7 were in the daily, intermittent and part daily treatment regimen groups. As the pharmacokinetic study was conducted during the intensive phase, during which patients in the part-daily regimen were receiving RMP daily, this group was combined with the daily group for analysis. Patients treated with the thrice-weekly regimen had significantly lower plasma C_{max} and $AUC_{0–24}$ and higher Cl of RMP than those treated with the daily regimen (Table). RMP concentrations were below the detectable limit at pre-dosing for 62% of patients at 24 h for daily dosing and for 80% at 48 h for intermittent dosing; the mean RMP concentrations were respectively 0.25 and 0.12 μg/ml; the differences were not statistically significant. The proportion of patients with RMP C_{max} below the reference range (<8.0 μg/ml) was 100% in the thrice-weekly and 85% in the daily arm; the difference was non-significant.

DISCUSSION

We observed lower RMP C_{max} and exposure in patients treated with the intermittent regimen than in those treated with a daily regimen among HIV-infected patients with TB. This was probably due to lower pre-dosing RMP concentrations in those treated intermittently; a low RMP concentration to start with could be a possible reason for patients in the intermittent arm to have low RMP C_{max} and exposure than those in the daily arm. The difference in total RMP exposure over a period of 1 week was quite large (respectively 205.8 and 62.1 μg/ml.h during daily and intermittent dosing). These findings suggest that the treatment schedule plays a vital role in preserving blood levels, which could potentially affect the efficacy of the regimen.

The relationship between plasma drug levels and anti-tuberculosis treatment outcome remains debatable. Treatment outcome is driven by multiple factors, such as bacillary load, type of strain, virulence, minimal inhibitory concentration in relation to drug levels, duration of infection, extent of disease, immune status and nutritional status. While Narita et al. did not find an association between TB recurrence and the serum levels of anti-tuberculosis drugs,[6] Pasipanodya et al. reported that low RMP and INH C_{max} preceded acquired drug resistance and concluded that low drug exposures were predictive of clinical outcomes in TB patients.[7] Low RMP C_{max} has been observed to influence treatment outcomes and/or acquired RMP resistance.[8,9] Furthermore, the risk of failure, relapse and acquired RMP resistance

among HIV-infected TB patients was observed to correlate with RMP dosing schedules, and was higher in those treated with intermittent regimens.[10] Persistently low concentrations of some drugs could provide a favourable nidus for drug-resistant mutants of *M. tuberculosis* that could eventually lead to the emergence of drug resistance. As treatment progresses, such patients could manifest delayed smear conversion that could subsequently lead to treatment failure or relapse and acquired RMP resistance.

Our study highlights that, although RMP C_{max} was below the reference range in the majority of the patients, the higher pre-dosing and C_{max} achieved during daily anti-tuberculosis treatment appear to pose a distinct advantage, as evidenced by higher exposure. This could enhance RMP's exposure-dependent killing of mycobacteria, thereby maximising benefits.

Acknowledgements

The authors thank all the patients for participation in the study, V Sudha for drug estimations, S Venkatesh for counselling and follow-up of patients; and S S Muthu, N Logeshwaran, S Rajasekaran and other clinic staff for blood collection and for carrying out the study.

Funding was provided by the United States Agency for International Development through the World Health Organization South-East Asian Regional Office, New Delhi, India.

Conflicts of interest: none declared.

References

1 Vernon A, Burman W, Benator D, et al. Acquired rifampicin mono-resistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Lancet 1999; 353: 1843–1847.

2 Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomised clinical trial. Am J Respir Crit Care Med 2010; 181: 743–751.

3 Gurumurthy P, Ramachandran G, Kumar Hemanth A K, et al. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced HIV disease. Antimicrob Agents Chemother 2004; 48: 4473–4475.

4 Perlman D C, Segal Y, Rosenkranz S, et al. The clinical pharmacokinetics of rifampicin and ethambutol in HIV-infected persons with tuberculosis. Clin Infect Dis 2005; 41: 1638–1647.

5 Hemanth Kumar A K, Chandra I, Ramachandran G, Silambu Chelvi K, Victor L, Gurumurthy P. A validated high performance liquid chromatography method for the determination of rifampicin and desacetyl rifampicin in plasma and urine. Indian J Pharmacol 2004; 36: 231–233.

6 Narita M, Hisada M, Thimmappa B, et al. Tuberculosis recurrence: multivariate analysis of serum levels of tuberculosis drugs, human immunodeficiency virus status and other risk factors. Clin Infect Dis 2001; 32: 515–517.

7 Pasipanodya J G, McIlleron H, Burger A, Wash P, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis. J Infect Dis 2013; 208: 1464–1473.

8 McIlleron H, Wash P, Burger A, Norman J, Folb P I, Smith P. Determinants of rifampin, isoniazid, pyrazinamide and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother 2006; 50: 1170–1177.

9 Mehta J B, Shantaveerappa H, Byrd Jr R P, Morton S E, Fountain F, Roy T M. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. Chest 2001; 120: 1520–1524.

10 Li J, Munsiff S M, Driver C R, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997–2000. Clin Infect Dis 2005; 41: 83–91.

RESUME

Nous avons comparé la pharmacocinétique de la rifampicine (RMP) lors d'un traitement antituberculeux quotidien et intermittent (trois fois par semaine) chez des patients tuberculeux infectés par le virus de l'immunodéficience humaine. Les patients traités par un protocole trihebdomadaire ont eu une concentration maximale et l'aire sous la courbe de la concentration plasmatique de 0 à 24 h significativement plus élevées et une clairance orale plus élevée de la RMP que ceux traités par le protocole quotidien ; les valeurs médianes étaient de 3,7 et 6,4 µg/ml ($P < 0,001$), de 20,7 et 29,4 µg/ml.h ($P = 0,03$) et de 21,7 et 15,3 ml/min ($P = 0,03$), respectivement.

RESUMEN

En el presente estudio se comparó la farmacocinética de la rifampicina (RMP) durante el tratamiento antituberculoso diario e intermitente (tres veces por semana), en pacientes coinfectados por el virus de la inmunodeficiencia humana. En comparación con los pacientes tratados con el régimen diario, los pacientes que recibieron el régimen intermitente presentaron valores medianos significativamente más bajos de la concentración máxima (3,7 µg/ml contra 6,4 µg/ml; $P < 0,001$) y el área bajo la curva de concentración plasmática y tiempo 0–24 h (20,7 µg/ml.h contra 29,4 µg/ml.h; $P = 0,03$) y una depuración más rápida de la RMP oral (21,7 ml/min contra 15,3 ml/min; $P = 0,03$).