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Correspondence

Saquinavir and rifampicin for tuberculosis and AIDS: new considerations

Concomitant tuberculosis (TB) and HIV therapy is of concern for health care providers, and particularly for clinicians who have to deal on a daily basis with the problem recently highlighted by Gray et al.[1] Now, without the possibility of using the saquinavir-ritonavir combination, we have no therapeutic option left for antiretroviral-experienced patients, given that lopinavir-ritonavir has not yet been tested in TB-HIV patients.[2]

In Brazil, we have 5 years of experience in treating TB-HIV patients with ritonavir 400 mg–saquinavir 400 mg, and although some patients did experience toxicity related to the combination of protease inhibitors (PIs), the clinical and virological benefits are clear. Our results were presented at the 3rd IAS Conference. Hepatoxicity was observed in 4/20 patients, all of whom recovered after discontinuation of therapy.[3]

Some points about the study that resulted in contraindication of concomitant saquinavir therapy with rifampicin should be highlighted: this study was for a new drug formulation (saquinavir 500 mg tablets), unlike the hard and soft gel capsules used in clinical practice, and probably with different bioavailability; it was performed in healthy volunteers who usually present lower tolerance than antiretroviral-experienced HIV patients; the group that presented more adverse events (hepatotoxicity) had initiated therapy with rifampicin for 14 days, after which combined ritonavir and saquinavir was added (as for our TB patients). In this group, 65% (11/17 subjects) hepatotoxicity was observed, in contrast with the other arm (35%) which initiated therapy with the PI combination, adding rifampicin after 14 days. The data from the study suggested that a rifampicin metabolite (25-desacetylrifampicin) could be responsible for the difference in toxicity observed in both arms. We were very intrigued by this finding, as we could find no paper associating the concentration of this metabolite with rifampicin toxicity. Because the trial was discontinued early, the data presented could not definitively support this hypothesis.[4]

A paper was recently published by Ribera et al. evaluating saquinavir 1600 mg and ritonavir 200 mg once daily; only two cases of hepatoxicity were registered.[5] The question is: why we do not see this hazardous effect in real life? Why do we have to accept the contraindication of saquinavir? Most peers that participated in the Brazilian Consensus (our local guidelines) have been afraid to recommend the use of saquinavir since the FDA contraindicated its use. They argue that disagreement with this position could put the group in legal jeopardy.

We should not disregard 5 years of experience with one drug, and further studies should be performed to clarify this issue before contraindicating the use of saquinavir. We are very glad to see the letter from Gray et al.,[1] and to find that many other people, other than Brazilians, are discussing this problem.

Thiago Silva Torres
Valeria Cavalcanti Rolla
Instituto de Pesquisa Clínica Evandro Chagas–Fundação Oswaldo Cruz
Infectious Diseases Department
Rio de Janeiro, Brazil
ttorres@ipec.fiocruz.br

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In reply

The clinical challenge of managing tuberculosis-HIV-co-infected patients is, as noted by Rolla and colleagues, common in resource-constrained settings. They suggest that their own experience over 5 years may be useful to inform the development of guidelines for TB-HIV co-treatment.

In the absence of adequate good quality data, this approach may indeed suffice. For example, the 5th edition of the South African Aid for AIDS (AfA) Clinical Guidelines, published in 2005, stated that 'rifampicin has significant drug interactions with the

protease inhibitors and NNRTIs', and that '[w]hen antiretroviral therapy is indicated it is preferable to use a regimen which does not interact significantly with rifampicin'.[1] The table in these guidelines gave two alternative protease inhibitor-containing regimens: lopinavir/ritonavir 400 mg/100 mg twice a day, plus additional ritonavir 300 mg twice a day (noting that the additional ritonavir should be started 2 days after the co-formulated lopinavir/ritonavir at 100 mg twice a day, increasing every 2 days by 100 mg twice a day up to ritonavir 300 mg twice a day and then stopped 1 week after stopping rifampicin) and ritonavir plus saquinavir, both at 400 mg twice a day.

The question is whether the experience of clinicians can justify ignoring the contraindication stipulated by the manufacturer of saquinavir (Roche Pharmaceuticals) and accepted by the US Food and Drug Administration. Rolla et al., and the AfA, have pointed to the difference in dosing regimen and the formulation of saquinavir used. Rolla et al. initiated highly-active antiretroviral therapy 30 days after commencing tuberculosis therapy.[2] Of the 20 patients treated with the saquinavir-ritonavir 400/400 mg twice a day regimen, 15 dropped out. The IAS abstract noted that 14/15 drop-outs were due to adverse effects, of which hepatic and gastrointestinal were the most frequent. In their letter, however, it is stated that only 4/20 developed hepatotoxicity and that all recovered after therapy was discontinued. No details are provided on how anti-tuberculosis therapy, and in particular rifampicin and isoniazid dosing, was altered, if at all.

Mention is made of the single-arm, prospective, multicentre, open-label pilot study reported by Ribera et al.[3] The dose used here, initiated after 2 months of TB therapy, was ritonavir 200 mg and saquinavir 1600 mg per day. Although only 2/32 patients discontinued therapy due to hepatotoxicity, 7/32 experienced virological failure. The median saquinavir trough concentration was 44% lower when used with rifampicin than without. The authors therefore concluded that this dosage regimen could not be recommended.

A recent review has confirmed that ritonavir is associated with a higher incidence of hepatotoxicity than the other protease inhibitors.[4] The incidence of liver enzyme elevations ranged from 11.7 to 27.3 per 100 patients exposed for ritonavir and from 11.6 to 32.1 for ritonavir/saquinavir.

While the inclusion of unregistered indications in guidelines has occurred in the past (a particular example being the use of misoprostol in the termination of pregnancy), we would caution against ignoring a contraindication that is accepted by a stringent medicines regulatory body, unless the evidence is overwhelming. We would therefore repeat our call for further studies, including pharmacokinetic studies, to address the ART options appropriate for resource-limited settings, and in particular, for co-administration with rifampicin-containing tuberculosis treatment.

Andy Gray*†
Salim S. Abdool Karim†‡
on behalf of the START Project
*Department of Therapeutics and Medicines Management
University of KwaZulu-Natal, Durban
†Centre for the AIDS Programme of Research in South Africa (CAPRISA)
University of KwaZulu-Natal, Durban, South Africa
‡Department of Epidemiology
Columbia University, New York, USA
e-mail: karims1@ukzn.ac.za

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Multidrug-resistant tuberculosis in India

Multidrug-resistant tuberculosis (MDR-TB) has emerged as a possible threat to tuberculosis control efforts worldwide. The current global concern in the treatment of tuberculosis (TB) is the emergence of resistance to the two most potent drugs, isoniazid (INH) and rifampicin (RMP). Technically, MDR-TB is caused by *Mycobacterium tuberculosis* resistant to both INH and RMP, with or without resistance to other drugs. Globally, about three per cent of all newly diagnosed patients have MDR-TB. The proportion is higher in patients who have previously received anti-tuberculosis treatment, reflecting the partial failure of programs designed to ensure complete cure of patients with tuberculosis.

I read with great interest the article by Santha et al. in the January issue of this *Journal* that reports the drug susceptibility profile of *M. tuberculosis* isolates from India.[1] In this study, 12% of previously treated patients showed resistance to INH and RMP. This

report mentioned that other parts of India have reported a high prevalence of MDR-TB. The reasons for the higher MDR resistance in other reports are further suggested to be due to the nature of patients in those specialized centers.[2,3] Recently, we reported drug resistance patterns in a referral chest disease institute in India which showed 2.2% resistance to only INH and RMP and 11.9% resistance to other first-line drugs along with INH and RMP.[4] I strongly feel that our report has strong relevance in this context which is completely overlooked and not disseminated to readers.

Tapen Dam
Department of Biology
Johns Hopkins University
Baltimore, MD, USA
e-mail: tdam1@jhmi.edu

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ERRATA

In the two articles by the same group published in the January and August 2006 issues of the IJTLD, entitled respectively 'Implementation of asthma guidelines in health centres of several developing countries' and 'Treatment outcome of asthma after one year follow-up in health centres of several developing countries', the author lists should have read as follows:

Ait-Khaled N, Enarson D A, Bencharif N, Boulahdib F, Camara L M, Dagli E, Djankine T K, Keita B, Karadag B, Ngoran K, Odhiambo J, Ottmani S E, Pham D L, Sow O, Yousser M, Zidouni N. Implementation of asthma guidelines in health centres of several developing countries. Int J Tuberc Lung Dis 2006; 10(1): 104–109.

Ait-Khaled N, Enarson D A, Bencharif N, Boulahdib F, Camara L M, Dagli E, Karadag B, Ottmani S E, Pham D L, Sow O, Yousser M, Zidouni N. Treatment outcome of asthma after one year follow-up in health centres of several developing countries. Int J Tuberc Lung Dis 2006; 10(8): 911-916.

A citation error occurred in the article entitled 'Efficiency of serial smear examinations in excluding sputum smear-positive tuberculosis', Mabaera B, Naranbat N, Dhliwayo P, Rieder H L. Int J Tuberc Lung Dis 2006; 10(9): 1030–1035.

Reference 2 should have read as follows: Urbanczik R. Present position of microscopy and of culture in diagnostic mycobacteriology. Zbl Bakt Hyg A 1985; 260: 81–87.