No evidence that rifampicin has glucocorticoid-like immunosuppressive properties leading to suppression of rat-splenocyte proliferation in vitro

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Sir,
Rifampicin (RIF) is a widely used antibiotic and is clinically very effective against a variety of organisms, including Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Legionella pneumophila. Furthermore, RIF is also very effective in the treatment of mycobacterial infections.1 In 1998, Calleja et al.2 reported that RIF might act as a non-steroid ligand and activator of the human glucocorticoid receptor. Using reporter gene assays, they demonstrated that RIF could not only induce the transcription of a gene controlled by a glucocorticoid responsive element, but also repressed the transcriptional activation of the IL-2 promotor.2 However, the results of Calleja et al. remain controversial. For example, no glucocorticoid-like side effects of RIF have been reported, although patients have been treated with RIF for >6 months.1 Moreover, Jaffuel et al.3 could not demonstrate an activation of the glucocorticoid receptor in A549 human alveolar cells.

RIF is also widely used to prevent infections in laboratory animals. For example, RIF is commonly used as a prophylaxis to prevent infection of medical devices or biomaterials that are tested in rats.4 Because the glucocorticoid receptors of rats and humans share a strong homology, it is reasonable to hypothesize that RIF might have glucocorticoid-like actions in rats.5 These glucocorticoid-like actions might include suppression of the immune system. This suppression of the immune system by RIF might interfere with results of animal experiments, because the rats might become vulnerable to viral infections or fungal opportunistic infections.

To test whether RIF did have immunosuppressive activity that RIF might act as a non-steroid ligand and activator of the human glucocorticoid receptor. Using reporter gene assays, they demonstrated that RIF could not only induce the transcription of a gene controlled by a glucocorticoid responsive element, but also repressed the transcriptional activation of the IL-2 promotor. However, the results of Calleja et al. remain controversial. For example, no glucocorticoid-like side effects of RIF have been reported, although patients have been treated with RIF for >6 months. Moreover, Jaffuel et al. could not demonstrate an activation of the glucocorticoid receptor in A549 human alveolar cells.

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in rats, we investigated whether RIF is capable of suppressing lymphocyte proliferation in vitro. For this purpose splenocytes of Bio-Breeding/Worchester rats were stimulated with 2 mg/L ConA and incubated with RIF or dexamethasone (DEX) in a concentration range from 0.01 to 1 μM. The specific glucocorticoid receptor antagonist RU486 was used to investigate whether the actions of RIF or DEX were mediated via the glucocorticoid receptor.

The figure shows the dose–response curve of DEX in the suppression of rat splenocyte proliferation. One micromolar DEX suppressed the splenocyte proliferation by 80%. In contrast, equimolar concentrations of RIF did not result in suppression of proliferation. Accordingly, the suppression of splenocyte proliferation by 1 μM DEX could be completely antagonized by 1 μM RU486. Interestingly, the combination of RU486 and DEX gives a slight, but significant stimulation of splenocyte proliferation. Combination of RIF and RU486 had no effect on the rat splenocyte proliferation.

The slight stimulation of the splenocyte proliferation by the combination of RU486 and DEX confirms the previous findings of Wiegers et al.6 In that study, Wiegers et al. demonstrated that occupation of the mineralocorticoid receptor by glucocorticoids stimulated rat lymphocyte proliferation in vitro. The fact that RIF itself does not suppress, or in combination with RU486 enhance, rat splenocyte proliferation in vitro indicates that RIF does not possess glucocorticoid-like activities mediated via the glucocorticoid receptor or the mineralocorticoid receptor.

Taken together, our observations give no indication that RIF under physiological circumstances in vitro has immuno-suppressive properties. These results further strengthen the findings of Jaffuel et al.3 and Raviglioni et al.,1 that RIF has no glucocorticoid-like actions leading to immuno-suppression. Therefore our results suggest that the current practice in the use of RIF in animal experiments need not be changed.

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References