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EDITORIAL

Rifabutin induced multinucleated hepatocytes in rats: an overview with future prospects

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To the Editor:

Rifabutin is a spiropiperidyl rifamycin that has many properties of the rifamycin family. Formerly, rifabutin was termed as ansamycin or LM 427 and recognized in 2009 as an essential medicine by the WHO 17th Expert Committee. Rifabutin is an antibiotic, which is particularly active against mycobacterium tuberculosis, non-tuberculous mycobacteria, pneumococcal, staphylococcal meningitis, *Staphylococcus aureus*, multi-drug resistance gam-negative bacilli, mycobacteria in AIDS patients, neisseria gonorrhoeae, helicobacter pylori, toxoplama gondii, neisseria meningitides, haemophilus influenzae, haemophilus ducreyi, group A streptococci, and lung cancer [1]. Historically, in 1993, the long-term toxicity study of rifabutin on rat, mice, and monkeys confirmed dose- and gender-related multinucleated hepatocytes (MNHs) in rats only after 5 weeks of treatment [2]. MNHs seem to be specific to rats and being more evident in males than females [2]. Furthermore, the official monograph of Mycobutin® (rifabutin 150 mg capsules USP) which was updated and revised in 2015 noted that the daily administration of rifabutin or alternate days induced through unclear mechanism MNHs in male rats in all dose groups and in female rats at 28 and 80 mg/kg/day only. Moreover, rifabutin stimulated liver hypertrophy with raised enzymes ALT, AST, bilirubin, triglycerides, and cholesterol in all other species (http://www.pfizer.ca). However, there is still unknown mechanism about that evidence. Thus, here we would like to shed light on one of the possible mechanisms which may responsible for that phenomenon. Rifabutin is a promising starting compound for producing a clinically approach of B cell lymphoma 6 protein (BCL6) inhibitor due to their long half-life, high lipid solubility, and wide tissue penetration [3]. In this respect, rifabutin interacts with BCL6-POZ domain which necessary for suppression of protein activity and functional interaction of BLC6 with SMRT corepressor and that proved through obviously largest chemical shift perturbations by studying nuclear magnetic resonance (NMR) and crystal structure of BLC6 complex with rifabutin in 2014 [4, 5]. Interestingly, the BCL6 expression in rat liver is higher in male than female [6, 7]. Substantially, in the toxicity study of rifabutin, MNHs were also noticed in more than one-year old untreated control rats [2]. Therefore, it seems that phenomenon is linked to aging. There is now significant evidence that cellular senescence is a crucial mechanism of aging and age-related conditions. It is well known that cell senescence is mostly accompanied by cell morphological changes such as become large, flat, and multinucleated. In addition, BCL6 is a potent inhibitor of senescence and beats the response of senescence downstream p53 via a process that demands cyclin D1 expression induction [8]. Consequently, BCL6 overrides the cellular senescence higher in male than in female rats. Hence, rifabutin may target BCL6 in rat liver and induces MNHs that are more visible in male than female. Moreover, research is needed to further evaluate the chronic toxicity studies of rifabutin which concern its interaction with BCL6 and SMRT in rats' liver.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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