TITLE: Estimating Ribavirin Plasma Exposure: Genetics or Therapeutic Drug Monitoring?

Authors:
Antonio D'Avolio, BSc, MSc, SM
Jessica Cusato, BSc, MSc
Andrea Calcagno, MD, DTM&H
Giovanni Di Perri, MD, DTM&H, PhD

Unit of Infectious Diseases, University of Turin, Department of Medical Sciences, Amedeo di Savoia Hospital, Turin, Italy

Words (excluding references and legend)**:** 484

Number of Figures: 1

Corresponding Author: Antonio D'Avolio, (BSc, MSc, SM); Tel. +39.011.4393979, Fax: +39.011.4393882; e-mail: antonio.davolio@unito.it

Conflicts of interest: The authors disclose no conflicts.

Dear Sir,

Rau and colleagues described the impact of genetic polymorphisms in SLC28 genes encoding for concentrative nucleoside transporter 2 (CNT2) and 3 (CNT3) and inosine triphosphatase (ITPA) variants on ribavirin (RBV) serum levels, hemoglobin drop and therapeutic response in patients with HCV infection [1]. In this paper they cited our observation that single nucleotide polymorphism (SNP) in the SLC28A2 encoding region (rs11854484) was an independent predictor of sustained virological response (SVR) [2, 3]. Our hypothesis was that this effect could be explained by the different ability of CNT2 forms to internalize RBV within cells, and not with a direct effect on RBV plasma levels.

In the era of dual PEG-interferon (PEG-IFN)/RBV therapy, most of the studies that investigated the role of RBV pharmacokinetics (Pk) found a clear association between higher RBV exposure and a higher chance of both SVR and anaemia, as expected on the basis of the recognized proportionality between RBV daily dose and these two outcomes [4]. Even in most recent studies, where patients were stratified according to human genetic polymorphisms, RBV Pk retained its significant role in predicting both efficacy and toxicity in PEGIFN/RBV intakers [2, 3, 5-7]. While the need for RBV as part of new triple therapies has been proven in development trials [8], it remains to be determined whether RBV Pk has still any impact on treatment outcomes with highly effective direct acting antivirals (DAAs). Then, the ability to early predict with genetics or therapeutic drug monitoring (TDM) ribavirin plasma concentrations at steady state retains its clinical importance.

Rau and colleagues described the association between CNT2 SNPs and RBV plasma concentrations. It should be noted that these PK/PG analyses were conducted on 67 patients only, without dose correction verification, including patient with modified dosage. In addition, they only reported a trend for statistical significance for the association of RBV concentration and SLC28 genotypes [1]. Our observations did not support this association [2, 3]: CNT2 SNPs were not associated with plasma RBV concentrations (after 4 weeks) while adjusting for the dose pro kilogram and for dose reduction, and only using several SNPs [rs11854484, rs2413775 and rs1060896] in “unfavorable” (for lower ribavirin concentrations) combinations (on 186 HCV+ patients) it was possible to demonstrate a statistical significance ($p=0.009$) [Figure 1]. On the contrary week 4 RBV plasma exposure seems to be nicely predicted by week 2 concentrations suggesting a possible early use of TDM to adjust the drug exposure both to enhance efficacy and reduce toxicity ($p <0.001$) [9, 10].

We therefore have no clear answer to the question whether genetic SLC28 transporter polymorphisms predict ribavirin plasma levels. If RBV plasma exposure maintains its clinical impact in new anti-HCV treatment studies comparative evaluations of pharmacogenetics vs. early pharmacokinetics are warranted. It should also be highlighted that the cost of a single early (2 weeks) determination of ribavirin plasma concentration does not significantly impact on the overall

expenditure associated to the use of (triple) anti-HCV therapy and may well contribute to a fruitful tailored management.

References

[1] Rau M, Stickel F, Russmann S, Manser C, Becker P, Weisskopf M, et al. Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. J Hepatol 2012.

[2] D'Avolio A, Ciancio A, Siccardi M, Baietto L, Simiele M, Patanella S, et al. SLC28A2 65C > T PREDICT SUSTAINED VIROLOGICAL RESPONSE IN PATIENTS WITH HEPATITIS C TREATED WITH INTERFERON AND RIBAVIRIN, CONSIDERING ALL HCV GENOTYPE AND GENOTYPE 1/4. Journal of Hepatology 2010;52:S463-S463.

[3] D'Avolio A, Ciancio A, Siccardi M, Smedile A, Simiele M, Cusato J, et al. Negative predictive value of IL28B, SLC28A2 and CYP27B1 SNPs and low RBV plasma exposure for therapeutic response to PEG/IFN-RBV treatment. Ther Drug Monit 2012;34:722-728.

[4] Snoeck E, Wade JR, Duff F, Lamb M, Jorga K. Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin. Br J Clin Pharmacol 2006;62:699-709.

[5] D'Avolio A, Ciancio A, Siccardi M, Smedile A, Baietto L, Simiele M, et al. Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associate anemia in patients receiving standard anti-HCV treatment. Ther Drug Monit 2012;34:165-170.

[6] D'Avolio A, Ciancio A, Siccardi M, Baietto L, Simiele M, Cariti G, et al. Ribavirin pharmacokinetics and interleukin 28B plus cytochrome P450 27B1 single-nucleotide polymorphisms as predictors of response to pegylated interferon/ribavirin treatment in patients infected with hepatitis C virus genotype 1/4. Hepatology 2011;54:2279.

[7] Aguilar Marucco D, Gonzalez de Requena D, Bonora S, Tettoni C, Bonasso M, De Blasi T, et al. The use of trough ribavirin concentration to predict sustained virological response and haematological toxicity in HIV/HCV-co-infected patients treated with ribavirin and pegylated interferon. J Antimicrob Chemother 2008;61:919-924.

[8] Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839-1850.

[9] Caviglia G, D'Avolio A, Ciancio A, De NicolÃ² A, Boglione L, Abate M, et al. F-33 Early ribavirin plasma concentration and ITPA polymorphisms as determinants of anemia after one month of anti-HCV therapy. Digestive and Liver Disease 2012;44:S42.

[10] Slavenburg S, Huntjens-Fleuren HW, Dofferhoff TS, Richter C, Koopmans PP, Verwey-Van Wissen CP, et al. Ribavirin plasma concentration measurements in patients with hepatitis C: early ribavirin concentrations predict steady-state concentrations. Ther Drug Monit 2011;33:40-44.

Figure 1. Lower plasma concentrations of ribavirin were related with higher number of "unfavorable" CNT2 SNPs (rs11854484 [TT], rs2413775 [AT/TT] and rs1060896 [CC]). Only the difference between the group "0" and "3" is statistically significant (p=0.006).