Elimination half-life may explain the relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1.

Clinical Infectious Diseases

Comment on "The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of Hepatitis C Virus Genotype 1"

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Corresponding Author:	Andrea Calcagno Infectious Diseases Unit, University of Torino, Department of Medical Sciences Torino, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Infectious Diseases Unit, University of Torino, Department of Medical Sciences
Corresponding Author's Secondary Institution:	
First Author:	Andrea Calcagno
First Author Secondary Information:	
Order of Authors:	Andrea Calcagno
	Lucio Boglione
	Francesco Giuseppe De Rosa
	Giovanni Di Perri
	Stefano Bonora
Order of Authors Secondary Information:	
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Cover Letter
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Università degli Studi di Torino
Ospedale "Amedeo di Savoia"
C.so Svizzera 164 – 10149 Torino
CLINICA DI MALATTIE INFETTIVE
Direttore Prof. *Giovanni Di Perri*

Torino, 23rd December 2012

Dear Editor,

Please find as online submission our manuscript entitled Comment on "The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of Hepatitis C Virus Genotype 1" to be considered for publication in Clinical Infectious Diseases.

We appreciated the analysis by Kirean and colleagued trying to assess the efficacy of telaprevir and boceprevir in the absence of direct comparison trials. We suggest that the observed superiority in telaprevir recipients could be justified by the drug longer elimination half.life and therefore forgiveness. We therefore apply what we learnt from antiretroviral treatment experience and we suggest that adherence should be taken into account, measured and enhanced by clinicians and researchers.

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The contact author is:

Andrea Calcagno,
Clinica Univeristaria di malattie Infettive Ip, Ospedale Amedeo di Savoia,
C.so Svizzera 164, 10149, Torino, Italy
t. 00390114393884
f. 00390114393942
andrea.calcagno@unito.it

The alternative contact author is:

Giovanni Di Perri,

Clinica Univeristaria di malattie Infettive IIp, Ospedale Amedeo di Savoia,
C.so Svizzera 164, 10149, Torino, Italy
t. 00390114393828
f. 00390114393942
giovanni.diperri@unito.it

We hope that this manuscript can be of interest to the readers of CID, and look forward to receiving from you.

Yours truly.

Dr. A. Calcagno

Comment on "The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of Hepatitis C Virus Genotype 1"

Calcagno Andrea, Boglione Lucio, De Rosa Francesco Giuseppe, Di Perri Giovanni and Bonora Stefano

Infectious Diseases Unit, University of Torino, Department of Medical Sciences, Torino Italy

Comment Letter

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Corresponding Author:

Andrea Calcagno,
c/o Ospedale Amedeo di Savoia,
Clinica Universitaria I piano
C.so Svizzera 164
10159, Torino, Italy
+390114393884, fax +390114393818
andrea.calcagno@unito.it

Dear Editor,

in their very comprehensive meta-analysis Dr. Kieran and co-workers compared the efficacy of telaprevir and boceprevir as third agents in the treatment of chronic HCV hepatitis; they found a significantly greater efficacy rate for telaprevir in the specific setting of prior relapsers as compared to standard pegylated interpheron/ribavirin (PegIFN/RBV) therapy [1]. Such a meta-analysis is so far the only attempt to compare the two new anti-HCV antivirals, which have been released into the market without any preference for either agent in treatment recommendations [2]. A number of parameters have been proven to influence the outcome of anti-HCV treatment, such as genetic variation in *IL28B*, the type of PegIFN administered, baseline HCV-RNA, RBV pharmacokinetic exposure and degree of liver fibrosis. As stated by the Authors, dependency of the treatment outcome on the third drug may be thus be rather variable, and even of borderline significance when multiple favourable factors coincide in the same patient. We think that further to what suggested by the Authors in terms of possible reasons accounting for the higher efficacy of telaprevir in prior relapsers, its longer elimination half-life ($t_{1/2}$, 9-11 hours) as compared to boceprevir (3.4 hours) should also be taken into consideration [3,4]. In anti-HIV therapy a longer half-life is the major determinant of what we call "forgiveness", such as the property of maintaining effective concentrations in spite of a missed dose of the drug/regimen [5]. In the field of antiretroviral therapy, where numerous head-to-head comparisons have been made, a tendency to a better virological outcome is almost always recognizable in favour of the regimen containing the drug/s with longer half-life [6-8], with the notable exception of integrase inhibitors (that being associated with a faster viral clearance may compensate

for the drug shorter half-life) [9]. Although patients' adherence has been far less characterized in the HCV setting than in antiretroviral therapy, we might reasonably envisage how patients under triple anti-HCV therapy taking oral drugs three times daily are at risk of suboptimal adherence. Supposing an equal degree of non-adherence, effective pharmacokinetic exposure of telaprevir persist longer than in case of boceprevir intake when a dose is missed, thus allowing a greater chance of maintaining adequate antiviral concentration despite of irregular drug intake. This pharmacokinetic property of telaprevir has been recently further testified by the successful validation of twice daily intake of the drug at equal total daily dose [10]. Since controlled head-to-head comparative trials between telaprevir and boceprevir are unlikely to be performed (and might soon lose interest with the new anti-HCV drugs being developed) the meta-analytic comparison carried out by the Authors might remain the sole to rely upon. Based on these considerations we believe that whenever patient's adherence is perceived to be particularly at risk, the choice of telaprevir might provide an advantage in terms of pharmacokinetic coverage.

Andrea Calcagno, MD, DTM&H

Lucio Boglione, MD

Francesco Giuseppe De Rosa, MD

Giovanni Di Perri, MD, DTM&H, PhD

Stefano Bonora, MD

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Transparency Declarations

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