
Correspondence: Diederek van de Beek, MD, PhD, Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, PO Box 22680, 1100DD Amsterdam, The Netherlands (d.vandebeek@amc.uva.nl).

Clinical Infectious Diseases® 2015;61(4):664–5 © The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/civ228

Reply to Brouwer and van de Beek

To the Editor—We appreciate Brouwer and van de Beek’s thoughtful comments to our registry study of acute bacterial meningitis (ABM) [1]. The large sample size enabled multivariate analyses and adjustment for relevant confounders showing earlier treatment and favorable clinical outcome after guideline revision deleting impaired mental status as a contraindication for immediate lumbar puncture (LP) in cases without signs of a cerebral mass lesion or impending herniation. The rationale for this revision has been reviewed in detail [2]. Brouwer and van de Beek raise some concern about the recommendation to revise current international guidelines [3, 4].

We demonstrated that LP in unconscious patients with ABM was not associated with any risks, consistent with other reports [5–7]. However, we agree that in cases with suspected ABM, several differential diagnoses, not included in the present study, should be considered, weighing possible risks with immediate LP against potential risks associated with delayed LP due to prior computed tomography (CT) [2, 8–11]. International guidelines are based on the Hasbun et al study in which specified clinical features predicted abnormal CT findings, not necessarily contraindicating LP [9]. On the contrary, Gopal et al showed that the clinician’s overall impression is the strongest positive predictor of CT-identified lesions contraindicating LP [8]. Too many CTs are performed, and adherence to the international guidelines is poor [12].

Brain abscess, the most important differential diagnosis, is often associated with focal neurological signs and a longer duration of cerebral symptoms [13]. The risk of LP-induced herniation in patients with brain abscess is difficult to assess because information about clinical findings temporally related to LP have seldom been clarified. Brouwer et al estimated this risk at 7% [13], whereas figures around 1%–2% have been reported by others [4, 14]. Furthermore, these figures are probably even lower in patients without focal neurological signs, and this risk should be balanced against the indisputable risk of delaying ABM treatment, with an increase in mortality of 1%–4% per hour of delay [1, 15].

There are pros and cons regarding the inclusion of patients in whom the diagnosis was made without cerebrospinal fluid (CSF) analysis. This patient group included some of the most severely ill with impending herniation, and to increase the external validity of the study, we included these patients in the outcome analysis. Our results did not change after excluding these patients.

The physicians were asked to fill out the questionnaire during their patient’s hospital stay. Because new guidelines were implemented in 2004 as well as in 2009, it is unlikely that physicians were tempted to state that they complied more with the guidelines during 2010–2012 than during 2005–2009. The recommendations to start corticosteroids together with antibiotics and to consider intracranial pressure monitoring were introduced in 2004. Similar use of these adjunctive therapies was observed between the 2 periods.

We fully agree to encourage every attempt to shorten time to treatment in patients with ABM. CSF analyses are often the key to rapid treatment in clinical practice, and LP before CT is associated with significantly earlier treatment and a favorable outcome [1, 16]. Available data and evidence warrant a revision of the current international guidelines, toward promoting early LP.

Note
Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Martin Glimåker,1 Bibi Johansson,1 Örjan Grindborg,2 Matteo Bottai,2 Lars Lindquist,1 and Jan Sjölin3
1Unit for Infectious Diseases, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, and 3Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, and 2Section of Infectious Diseases, Department of Medical Sciences, Uppsala University, Sweden

References
Hepatitis C Virus RNA Levels During Interferon-Free Combination Direct-Acting Antiviral Treatment in Registrational Trials

TO THE EDITOR—We read with interest the unexpected findings by Sidhanthan et al that indicate that detected or quantifiable hepatitis C virus (HCV) RNA at the end of direct-acting antiviral (DAA) treatment does not preclude sustained virologic response (SVR12) [1]. Using the Abbott HCV real-time assay (lower limit of quantitation [LLOQ], 12 IU/mL), the authors reported that among patients treated with sofosbuvir + ledipasvir ± GS–9669 or GS–9451 for 6 or 12 weeks, HCV RNA was detected (<LLOQ or ≥LLOQ) or quantifiable in 29/59 (49%) and 6/59 (10%) patients, respectively, and all but 1 patient achieved an SVR12.

To compare the results by Sidhanthan et al with those obtained in other DAA trials, we reanalyzed HCV RNA data from 12 registrational trials of interferon-free, combination DAA treatments [2–4] to assess the frequency of HCV RNA detection at the end of treatment among patients who achieved SVR12. In these trials, the Roche COBAS TaqMan HCV v1.0 assay (LLOQ = 43 IU/mL) was used, and the regimens were dosed for 8 to 24 weeks in various patient populations. HCV RNA was detected (<LLOQ or ≥LLOQ) at the end of treatment with the Roche v2.0 assay in only 12/3671 (0.3%) patients who achieved SVR12 (Table 1). Censoring patients who received <4 weeks of treatment or who experienced confirmed virologic breakthrough, a total of 22 patients with detected HCV RNA at the end of treatment were identified from these trials, of whom 12 (55%) achieved SVR12. While these results indicate detected HCV RNA at the end of treatment did not preclude SVR12, they do reflect a higher virologic failure rate than was observed in the general trial populations. Furthermore, for all but 1 of the SVR12-achieving patients, the detected or low quantifiable HCV RNA result was transient, preceded and followed by HCV RNA target-not-detected results, perhaps reflecting nonreproducible sampling of extremely low-level HCV RNA.

The authors’ use of the Abbott assay, which has been reported to be more sensitive in detecting low-level HCV RNA during treatment [5], likely contributed to a higher rate of detected or quantifiable HCV RNA relative to the larger DAA registrational trials. However, the on-treatment HCV RNA results reported by the authors using the Roche COBAS TaqMan HCV v1.0 assay (LLOQ = 43 IU/mL) also appeared higher than expected. For example, among patients treated with sofosbuvir + ledipasvir, 12/19 (63%) and 2/19 (11%) had detected or quantifiable HCV RNA at week 4, respectively. In contrast, among patients treated with sofosbuvir + ledipasvir ± ribavirin in the Ion-1, -2, and -3 trials, 268/1504 (18%) and 5/1504 (0.3%) patients had detected or quantifiable (≥25 IU/mL, Roche v2.0) HCV RNA at week 4, respectively (Table 1). Similarly low HCV RNA levels at week 4 were observed in other combination DAA trials. By week 8, HCV RNA was detected in <1% of patients overall. We encourage further analyses of HCV RNA levels using multiple sensitive assays in other short-course DAA combination studies, as these studies will help refine HCV kinetic models and guide future trial design.

Notes

Acknowledgments. The data analyzed for this report were submitted to the US Food and Drug Administration (FDA) in original or supplemental new drug applications for ledipasvir/sofosbuvir (Harvoni), ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak), and simprevir (Olysio). The authors acknowledge the study sponsors (Gilead Sciences Inc., AbbVie Inc., and Janssen Research and Development), investigators, and study volunteers as the source of these data.

Disclaimer. The views expressed in this report are those of the authors and do not necessarily represent official policy of the US FDA.

Potential conflicts of interest. All authors: No potential conflicts of interest.