Response-Guided Boceprevir-based Triple Therapy in HIV/HCV-coinfected Patients: The HIVCOBOC-RGT Study

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Background. The HIVCOBOC-RGT study (NCT01925183) was the first study to evaluate response-guided shortening of the duration of boceprevir (BOC)-based triple therapy in human immunodeficiency virus (HIV)/hepatitis C virus genotype 1-coinfected patients (HIV/HCV-GT1).

Methods. After 4 weeks of pegylated interferon-α-2a/ribavirin (PEGIFN/RBV) lead-in, patients with target-not-detectable HCV-RNA at week 8 (rapid virologic response; LI4W-W8U1ND) received 24 weeks of BOC/PEGIFN/RBV (total: 28 weeks [W28]). Patients with target-detectable HCV-RNA at week 8 received 44 weeks of BOC/PEGIFN/RBV (total: 48 weeks [W48]).

Results. Fourteen patients (67%) had LI4W-W8U1ND and were eligible for the shortened W28 arm, while 7 (33%) patients were allocated to the W48 arm. No breakthrough or relapse occurred in the W28 arm, resulting in a sustained virologic response (SVR12TND) rate of 100% (12/12). In the W48 arm, the SVR12TND was 50% (3/6), with 3 patients meeting the futility rule at treatment week 12. The preliminary overall SVR12TND rate was 83% (15/18). Serious adverse events were observed in 5 (24%) patients, with 2 (10%) patients requiring surgical treatment of abscesses.

Conclusions. The majority of HIV/HCV-GT1 were eligible for response-guided shortening of treatment duration to W28 and all of these patients had a SVR12TND. If second-generation direct-acting antivirals are not available, W28 of BOC-based triple therapy may be recommended.

Keywords. antiviral agents; boceprevir; hepatitis C; HIV; response-guided therapy.

Liver disease is the second leading cause of death in patients infected with human immunodeficiency virus (HIV) [1]. When compared to hepatitis C virus (HCV) monoinfection, HIV/HCV coinfection, observed in 25%–30% of European and US-American HIV-positive patients [2], was found to be associated with high rates of liver fibrosis progression [3, 4] and markedly higher risks of cirrhosis and end-stage liver disease [5]. As successful treatment of chronic hepatitis C is associated with a reduced risk for hepatic decompensation, liver-related, nonliver-related, and overall mortality [6, 7] in HIV/HCV-coinfected patients, optimizing antiviral therapy is of highest priority.

Throughout the last decade, the efficacy of dual-therapy with pegylated interferon plus ribavirin (PEGIFN/RBV) in HIV-positive patients has improved as a result of the individualization of treatment by response-guided therapy (RGT) [8]. However, especially in patients coinfected with the highly prevalent HCV-genotype (HCV-GT)1, efficacy of PEGIFN/RBV remained unsatisfactory, as underlined by a recent large, multicenter study with sustained virologic response (SVR24TND) rates as low as 21% [9].

The approval of first-generation direct-acting antiviral agents (DAAs), telaprevir (TVR) and boceprevir...
(BOC), has ushered in a new era in the treatment of HCV-GT1–infected patients [10]. Recently published phase IIa studies of triple therapy with TVR [11] and BOC [12] in combination with PEGIFN/RBV in treatment-naive HCV-positive individuals demonstrated substantially improved efficacy. While BOC-based triple therapy was found to be associated with additional side effects, as well as with an increase in the frequency and severity of established dual-therapy side effects [13, 14] in HCV-mono-infected patients, evidence from HIV-positive patients is very limited.

The practicability of response-guided triple therapy with TVR [15] and BOC [13] in HCV-mono-infected patients has previously been established. Based on the results of the SPRINT-2 trial [13], both the US and European label of BOC recommend a shortening of treatment duration in treatment-naive HCV-mono-infected patients with target-not-detectable (TND) HCV-RNA at treatment week 8, including a 4-week PEGIFN/RBV lead-in phase (rapid virologic response; LI4W-W8UTND). However, while RGT is currently used to individualize the duration of dual therapy in HIV-positive patients [8], response-guided triple therapy has not been investigated in this special population. Thus, current European AIDS Clinical Society (EACS) guidelines [16] recommend a fixed duration of 48 weeks of TVR/BOC-based triple therapy for HIV/HCV-GT1, similar to the 2 published studies on triple therapy in HIV-positive patients [11, 12]. However, a recently published case series suggests that a total treatment duration of 28 weeks of BOC-based triple therapy might be sufficient in HIV/HCV-GT1 with LI4W-W8U_TND [10].

The HIVCOBOC-RGT study evaluated the concept of response-guided shortening of the duration of BOC-based triple therapy in HIV/HCV-GT1.

PATIENTS AND METHODS

Study Design and Patients

Twenty-one HIV/HCV-GT1 were treated according to the HIVCOBOC-RGT study protocol (NCT01925183). The HIVCOBOC-RGT study was conducted at a tertiary center and the inclusion period was 1 year. In brief, inclusion requirements were: HIV infection with a CD4+ T-lymphocyte (CD4+) count >200 cells/µL and HIV-RNA <50 copies/mL on combined antiretroviral therapy (cART) with tenofovir/emtricitabine and raltegravir. Moreover, chronic infection with HCV-GT1, target-detectable HCV-RNA for more than 6 months, and a valid liver stiffness measurement or liver biopsy within 6 months prior to the enrollment were required. Patients coinfected with a HCV-GT other than HCV-GT1, patients with decompensated cirrhosis, and those with chronic liver disease other than hepatitis C were excluded. Further, ongoing alcohol abuse (defined as average daily alcohol consumption >50 g); ongoing intravenous drug use; or significant cardiac, pulmonary, or renal disease were defined as exclusion criteria.

Figure 1. Individualization of boceprevir (BOC)-based triple therapy by response-guided therapy (RGT). Abbreviations: HIV/HCV-GT1, human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients; LI4W-W8U_TND, target-not-detectable HCV-RNA at treatment week 8; SVR12_TND, sustained virologic response; W28, 28 weeks of treatment duration; W48, 48 weeks of treatment duration.

Antiviral Therapy

The nomenclature proposed by the Definitions/Nomenclature Working Group of the HCV Drug Development Advisory Group was adopted in reporting of virologic response [17]. Patients were treated with pegylated interferon-α-2a (180 µg) once a week and weight-based RBV doses ranging from 1000 to 1200 mg daily. After 4 weeks of PEGIFN/RBV lead-in (LI4W-W4), BOC was added (800 mg 3 times daily). Patients with LI4W-W8U_TND received 24 weeks of BOC/PEGIFN/RBV (total: 28 weeks [W28]), while patients with target-detectable HCV-RNA at treatment week 8 (LI4W-W8) received 44 weeks of BOC/PEGIFN/RBV (total: 48 weeks [W48]) (Figure 1). Treatment was discontinued due to futility rules in patients with HCV-RNA >100 IU/mL at treatment week 12 (LI4W-W12) or target-detectable HCV-RNA at treatment week 24 (LI4W-W24).

Interleukin 28B and Liver Stiffness Measurement

The interleukin 28B (IL28B) rs12979860 single nucleotide polymorphism (SNP) was analyzed as previously described [18]. Measurement of liver stiffness was performed by transient elastography, as previously described [19]. Significant liver fibrosis and cirrhosis were defined as liver stiffness values ≥7.2 kPa and ≥14.6 kPa, respectively [20].

Laboratory Assessments

Standard laboratory tests were used to assess hematological and biochemical parameters. HCV-GT as well as serum HCV-RNA and HIV-RNA levels were determined using commercially available assays (VERSANT HCV Genotype 2.0 Assay [LiPA] [Siemens, Vienna, Austria] and COBAS AmpliPrep/TaqMan HCV/HIV Test [Roche, Vienna, Austria]). The lower limits of quantification/detection were 15 IU/mL and 20 copies/mL for
HCV and HIV, respectively. High HCV-RNA was defined as baseline HCV-RNA level $>6 \times 10^5$ IU/mL [21–23].

**Primary Efficacy and Safety Endpoints**

The primary efficacy endpoint was sustained virologic response, defined as TND HCV-RNA 12 weeks after the end of treatment (SVR12\(_{\text{TND}}\)), while the incidence of adverse events (AEs) and serious adverse events (SAEs) was the primary safety endpoint. In addition, we assessed hematologic abnormalities, erythropoietin and granulocyte colony-stimulating factor analogue administration, blood transfusions, and the rate of treatment discontinuation due to AEs. Intention-to-treat analysis was applied to assess the primary outcome, SVR12\(_{\text{TND}}\), as well as LI4W-W8U\(_{\text{TND}}\).

**Statistics**

Statistical analyses were performed using IBM SPSS Statistics 21 (SPSS Inc, Chicago, Illinois). Continuous variables were reported as mean ± standard deviation or median (interquartile range), while categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic. Student t test was used for group comparisons of continuous variables when applicable. Otherwise, Mann–Whitney U test was applied. Group comparisons of categorical variables were performed using Fisher exact test. A P value ≤ 0.05 was considered as statistically significant.

Sensitivity and specificity were calculated using the MedCalc webpage (http://www.medcalc.org/calc/diagnostic_test.php, MedCalc Software, Ostend, Belgium).

**Ethics and Clinical Trial Registration**

This study was conducted with written informed consent from each participant and was approved by the local ethics committee of the Medical University of Vienna (number: 2055/2012). The “Individualized Triple-therapy Using Boceprevir in HIV-positive Patients With Hepatitis C (HIV/CBOC-RGT)” study was registered at EudraCT (number: 2012-005591-33) and ClinicalTrials.gov (identifier: NCT01925183).

**RESULTS**

**Study Population and Patient Characteristics**

All patients screened and eligible for this study were included. Two patients were screened but ineligible, as cART could not be changed to tenofovir/emtricitabine and raltegravir in these patients. The majority of patients were male (76%) with a mean age of 39.1 ± 8.9 years. All patients were on cART (tenofovir/emtricitabine plus raltegravir) with a mean CD4\(^+\) count of 545 ± 193 cells/µL (Table 1). Seventy-one percent were treatment-naïve, while 29% of patients had a relapse after a prior course of dual therapy. No prior partial or null responders were included in this study. None of the patients had previously received TVR/BOC-based triple therapy or any other DAA-based treatment. The majority of patients were infected with subtype 1a (86%), while 14% had subtype 1b. The mean HCV-RNA level was 6.64 ± 0.71 log IU/mL, with 86% of patients having high HCV-RNA. The distribution of IL28B rs12979860 SNP genotypes was: C/C, 29%; C/T, 48%; and T/T, 24%. Thirty-eight percent of patients had significant liver fibrosis, while no patient had cirrhosis.

**Rates of LI4W-W8U\(_{\text{TND}}\), SVR12\(_{\text{TND}}\) and their Predictors**

While information on LI4W-W8U\(_{\text{TND}}\) was available in all patients, who are still on treatment or in the follow-up period were not considered for the SVR12\(_{\text{TND}}\) analysis.

Fourteen patients (67%) had LI4W-W8U\(_{\text{TND}}\) and were eligible for the shortened W28 arm, while 7 (33%) patients were allocated to the W48 arm (Figure 1).

All patients (100% [12/12]) in the W28 arm achieved a SVR12\(_{\text{TND}}\). In the W48 arm, the SVR12\(_{\text{TND}}\) rate was (50% [3/6]), as 3 patients met the treatment-week 12 futility rule, resulting in an overall SVR12\(_{\text{TND}}\) rate of 83% (15/18) (Table 1, Supplementary Figure 1).

None of the baseline characteristics was predictive of LI4W-W8U\(_{\text{TND}}\) or SVR12\(_{\text{TND}}\). However, LI4W-W8U\(_{\text{TND}}\) was associated with a higher rate of SVR12\(_{\text{TND}}\) (W28: 100% vs W48: 50%; P = .025), although treatment duration was shortened to W28 in these patients (Table 1).

None of the patients had TND HCV-RNA at the end of the PegIFN/RBV lead-in phase (LI4W-W4U\(_{\text{TND}}\)), as HCV-RNA was quantifiable in all patients (LI4W-W4Q). HCV-RNA levels at the end of the PegIFN/RBV lead-in phase (treatment week 4; LI4W-W4) were lower in patients with (2.79 ± 1.52 log IU/mL), when compared to patients without LI4W-W8U\(_{\text{TND}}\) (5.98 ± 1.48 log IU/mL; P < .001) (Table 1, Supplementary Figure 1).

Moreover, a more pronounced viral load decline at LI4W-W8U\(_{\text{TND}}\) was observed among patients who achieved LI4W-W8U\(_{\text{TND}}\) (LI4W-W8U\(_{\text{TND}}\): −3.78 ± 1.35 vs No-LI4W-W8U\(_{\text{TND}}\): −0.795 ± 1.107 log IU/mL; P < .001). None of the 5 patients with a viral load decline at LI4W-W4 of less than −1.74 log IU/mL (LI4W-W4Q[<−1.74]) had LI4W-W8U\(_{\text{TND}}\) (sensitivity: 71%; specificity: 100%) (Table 2). In contrast, all of the 11 patients with a viral load decline at LI4W-W4 above −1.74 to −2.55 log IU/mL (LI4W-W4Q[>−2.55]) had LI4W-W8U\(_{\text{TND}}\) (sensitivity: 79%; specificity: 100%). Among 5 patients with a viral load decline of −1.74 to −2.55 log IU/mL, 3 (60%) patients had LI4W-W8U\(_{\text{TND}}\).

**Safety and Tolerability**

All patients had at least 1 AE, while SAEs occurred in 5 (24%) patients. Two patients (10%) were hospitalized due to surgical treatment of abscesses. Another AE related to bacterial infections was cellulitis in 3 cases (14%). These patients were treated with oral antibiotics as outpatients and their AEs were classified as nonserious. Moreover, the following SAEs were observed:
One patient underwent appendectomy for acute appendicitis during the follow-up period, 1 patient was hospitalized due to general disability, and 1 patient was hospitalized due to a pre-existing medical condition.

Except for the 2 previously mentioned patients requiring surgical treatment of abscesses, no treatment discontinuations due to AEs occurred. One of these patients had a SVR12TND. In the other patient, the SAE occurred simultaneously to LI4W-W12 and the patient met the LI4W-W12 futility rule at the time of treatment discontinuation.

Grade 3/4 hematologic abnormalities were observed in 5 (24%) patients, while 9 (43%) patients developed a CD4+ count <200 cells/µL. PEGIFN and RBV dose reductions were necessary in 1 (5%) and 10 (48%) patients, respectively. Erythropoietin and granulocyte colony-stimulating factor analogues were administered in 7 (33%) and 6 (29%) patients, respectively, and 2 (10%) patients received blood transfusions.

**DISCUSSION**

As response-guided TVR/BOC-based triple therapy has not been investigated in HIV-positive patients, current EACS guidelines [16] recommend a fixed duration of W48 of TVR/BOC-based triple therapy [11, 12]. However, this may be a pragmatic recommendation arising from the absence of studies investigating individualized treatment. Previous studies on triple therapy
Table 2. Association Between Viral Load Decline at Treatment Week 4 (LI4W-W4) and HCV-RNA Levels at Treatment Week 8 (LI4W-W8)

<table>
<thead>
<tr>
<th>Viral Load Decline at LI4W-W4</th>
<th>HCV-RNA Levels at LI4W-W8</th>
</tr>
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<tbody>
<tr>
<td>(log IU/mL)</td>
<td>(log IU/mL)</td>
</tr>
<tr>
<td>Q(0.28)</td>
<td>1.41 - LI4W-W8Q - W48</td>
</tr>
<tr>
<td>Q(0.08)</td>
<td>6.83 - LI4W-W8Q - W48</td>
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<tr>
<td>Q(0.07)</td>
<td>3.12 - LI4W-W8Q - W48</td>
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<td>Q(0.25)</td>
<td>5.16 - LI4W-W8Q - W48</td>
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<tr>
<td>Q(1.43)</td>
<td>1.45 - LI4W-W8Q - W48</td>
</tr>
<tr>
<td>Q(1.74)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(1.76)</td>
<td>1.08 - LI4W-W8Q - W48</td>
</tr>
<tr>
<td>Q(1.85)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(2.18)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(2.56)</td>
<td>1.3 - LI4W-W8Q - W48</td>
</tr>
<tr>
<td>Q(2.72)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(3.22)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(3.23)</td>
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<tr>
<td>Q(5.4)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
<tr>
<td>Q(5.71)</td>
<td>LI4W-W8UTND - W28</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; LI4W-W8UTND, target-not-detectable HCV-RNA at treatment week 8; LI4W-W8Q, quantifiable HCV-RNA at treatment week 8; LI4W-W12, treatment week 12; W28, 28 weeks of treatment duration; W48, 48 weeks of treatment duration.

in HIV-positive restricted to treatment-naive patients reported SVR12TND rates ranging of 63% [12] and 74% [11], which are very similar to the rates observed in treatment-naive, HIV-negative patients [13, 24]. Thus, DAAs may allow overcoming the diminishing effect of HIV coinfection on virologic response to interferon-based therapies, challenging the therapeutic paradigm of extended therapy duration in this special population [8, 16].

In our study, the majority of HIV/HCV-GT1 achieved LI4W-W8UTND and were eligible for response-guided shortening of treatment duration to W28. All of these patients had an SVR12TND, although this treatment arm comprised a substantial proportion of patients with negative baseline predictors of response to triple therapy [25, 26], including a significant proportion of treatment-experienced patients, as well as patients with HCV-subtype 1a, high HCV-RNA, IL28B non-C/C genotype, and significant liver fibrosis. Thus, if second-generation DAAs are not available, W28 of BOC-based triple therapy may be recommended for HIV/HCV-GT1 with LI4W-W8UTND.

Previous studies demonstrated excellent efficacy of dual therapy in patients with TND HCV-RNA at W4 (W4UTND) [22, 27]. Thus, in this subgroup, which accounts for about a quarter of HIV/HCV-GT1, the additional benefit of DAAs in terms of efficacy appears negligible. Interestingly, a recent meta-analysis suggests that in HCV-monoinfected patients with W4UTND, dual therapy may be even more effective [28]. Nevertheless, the use of BOC-based response-guided triple therapy allows for substantial shortening of treatment duration when compared to dual therapy, as a treatment duration of W48 is recommended in HIV/HCV-GT1 with W4UTND [16]. However, it is unclear whether the benefits of shortening treatment duration to W28 outweigh the additional, BOC-related side effects [13, 14] in these patients.

Nevertheless, in patients without LI4W-W4UTND but with LI4W-W8UTND (who accounted for 67% of our study population), response-guided shortening of the duration of BOC-based triple therapy may reduce the strain associated with antiviral therapy [29], as treatment regimens such as 72 weeks of dual therapy or W48 of TVR/BOC-based triple therapy are recommended in this subgroup [8]. However, our study did not have sufficient statistical power to detect clinically relevant differences in safety and tolerability between the treatment arms.

Interestingly, while none of the baseline characteristics was associated with LI4W-W8UTND, we observed a significant difference in viral load decline at LI4W-W4 between patients with LI4W-W8UTND and without. All patients with LI4W-W4Q [≥−2.55] had LI4W-W8UTND. This value is very similar to a previously established cut-off for the identification of HIV/HCV-GT1 with a good responsiveness to dual therapy [30]. Thus, the utility of a lead-in phase for assigning patients to dual therapy or TVR/BOC-based triple therapy should be emphasized, and viral kinetics during the lead-in phase may allow for early identification patients eligible for response-guided shortening of treatment duration to W28.

Importantly, none of the patients in our study had LI4W-W4UTND, which might be attributed to the high prevalence of negative baseline characteristics. This suggests that no easy-to-treat patients with a presumably high responsiveness to interferon-based therapies were included.

Information on safety of BOC-based triple therapy in HIV-positive patients is very limited. In our study, hematologic side effects were generally well managed by dose reduction of PegIFN or RBV and the use of hematologic growth factors. Blood transfusions were necessary in only 2 patients and no treatment discontinuation due to hematologic side effects was observed. However, we observed SAEs related to bacterial infections, requiring treatment discontinuation in 2 out of 21 patients. In addition, 3 cases of nonserious AEs due to bacterial infection were documented in our study. Importantly, all of the patients in our study who had preserved immune status and suppressed HIV-RNA, and did not have liver cirrhosis. In the ANRS-HC27 BocepreVIH study [31] investigating BOC-based triple therapy in HIV-positive treatment-experienced patients,
treatment discontinuation due to bacterial infections occurred only in 3 out of 64 patients, although 17% of patients included in this study had cirrhosis. However, similar to our study, SAEs related to bacterial infections (abscess/cellulitis, pneumonia, and sepsis) in patients without cirrhosis were reported. Thus, in HIV-positive patients, there might be high susceptibility for severe infectious complications during BOC-based triple therapy, which is not limited to patients with cirrhosis and additional risk factors [32, 33]. As bacterial infections may occur at any time point during antiviral therapy [34], the cumulative risk might rise with longer treatment durations. This provides an additional argument in favor of response-guided shortening of therapy duration.

Our findings, although limited by the small number of patients included in this study, provide important evidence for the individualization of triple therapy in HIV/HCV-GT1. As the availability of second-generation DAAs and interferon-free regimens is steadily increasing, it must be assumed that further prospective studies on triple therapy in HIV/HCV-GT1 will be rare. However, second-generation DAAs are not widely available and health insurance coverage of these upcoming regimens is limited, so triple therapy will continue to play a central role.

This is the first study to validate the concept of response-guided shortening of the duration of BOC-based triple therapy in HIV/hepatitis C genotype 1-coinfected patients (HIV/HCV-GT1). In summary, the majority of HIV/HCV-GT1 were eligible for response-guided shortening of treatment duration to 28 weeks (W28), and all of these patients had a sustained virologic response (SVR12TND). We observed 2 SAEs related to bacterial infections despite preserved immune status and the absence of cirrhosis. If second-generation direct-acting antivirals are not available, W28 of BOC-based triple therapy should be recommended for HIV/HCV-GT1 with (L148W-W8U198T).

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes


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Potential conflicts of interest. M. M. received honoraria for consulting from Janssen; payments for lectures from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, and Roche; as well as travel support from MSD and Roche. P. S. received payments for lectures from Roche and travel support from Janssen and Roche. B. A. P. received honoraria for consulting from MSD, payments for lectures from Roche, and travel support from Janssen and Roche. M. C. A. received honoraria for board membership and consulting from Gilead and MSD; and travel support from AbbVie, Gilead, and MSD. K. G. received honoraria for consultancy from Gilead; payments for lectures from Bristol-Myers Squibb and ViV; as well as travel support from Bristol-Myers Squibb, Gilead, and GlaxoSmitKline. M. T. received payments for lectures from Gilead, MSD, and Roche; and travel support from Gilead. M. P. received grants from Gilead, MSD, and Roche; honoraria for board membership and consultancy from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and MSD; as well as payments for lectures from Gilead, MSD, and Roche. T. R. received travel support from MSD and Roche as well as payments for lectures from Roche. All other authors report no potential conflicts.

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.

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