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Telaprevir-Based Triple Therapy for Chronic Hepatitis C Patients With Advanced Fibrosis

A Prospective Clinical Study

E. Ogawa; N. Furusyo; M. Nakamuta; E. Kajiwara; H. Nomura; K. Dohmen; K. Takahashi; T. Satoh; K. Azuma; A. Kawano; Y. Tanabe; K. Kotoh; S. Shimoda; J. Hayashi

Disclosures

Aliment Pharmacol Ther. 2013;38(9):1076-1085.

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Abstract and Introduction

Abstract

Background Antiviral treatment is recommended for chronic hepatitis C patients with advanced fibrosis to reduce and prevent cirrhosis-related complications.

Aim To evaluate the efficacy and safety of telaprevir (TVR)-based triple therapy for patients with advanced fibrosis in a clinical practice setting.

Methods This prospective, multicentre study consisted of 102 patients with advanced fibrosis (METAVIR score F3–4) who were infected with HCV genotype 1b. All received 12 weeks of TVR in combination with 24 weeks of pegylated interferon

(PEG-IFN) α 2b and ribavirin (RBV).

Results The sustained virological response (SVR) rate was 69.6% (71 of 102). Notably, for treatment-naïve and prior relapse patients the SVR rate was over 80%. Previous treatment response, interleukin 28B polymorphism (rs8099917) and rapid virological response (undetectable HCV RNA at week 4) were independently associated with SVR. To achieve SVR, an adequate dosage of PEG-IFN α 2b (\geq 1.2 μ g/kg/week) and RBV (\geq 7.5 mg/kg/day) is preferable; however, the mean weight-adjusted TVR dosage had little impact on treatment outcome. Although severe blood cytopenia and a dermatological disorder were frequently found, the rate of discontinuation due to adverse effects was 12.7%. The inosine triphosphatase CC allele (rs1127354) was independently associated with the development of severe anaemia, and lower serum albumin level ($<$ 35 g/L) was associated with the occurrence of infection.

Conclusions The great gain in the SVR rate by telaprevir-based triple therapy offsets the problems with adverse effects; thus, it should be considered as a potent treatment protocol for patients with advanced fibrosis, especially for those with treatment-naïve and prior relapse.

Introduction

The estimated global prevalence of hepatitis C virus (HCV) infection in 2004 was 2.2%,^[1] and 30–40% of patients with chronic hepatitis C will eventually develop cirrhosis, unless HCV is eradicated with anti-viral treatment.^[2, 3] The goal of therapy for chronic hepatitis C is to eradicate HCV infection, as indicated by sustained virological response (SVR), which has been associated with reduced development of hepatocellular carcinoma, hepatic decompensation, and prolonged survival.^[4–6] Therefore, anti-viral ^[7, 8]

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treatment should be initiated promptly for patients with advanced fibrosis (METAVIR score F3–4). However, advanced fibrosis lowers the chance of treatment success by non pegylated interferon, pegylated interferon-alpha (PEG-IFN α), and the combination of PEG-IFN α and ribavirin (RBV) for HCV genotype 1 patients.^[8–10]

Since 2011, the standard of care regimen for the treatment of HCV genotype 1 has been a combination of a non structural (NS) 3/4A protease inhibitor, PEG-IFN α , and RBV. The 2 first-generation NS3/4A protease inhibitors, telaprevir (TVR) and boceprevir, have been approved worldwide. In phase III trials, SVR rates have dramatically increased, especially for patients with prior relapse or no or mild fibrosis (METAVIR score F0–2).^[11–14]

Recently, the CUPIC study from France carried out in a clinical practice setting, showed a safety profile for TVR- and boceprevir-based triple therapy for cirrhotic patients.^[15] Our recent study suggested that inosine triphosphatase (ITPA) polymorphism (rs1127354) is useful for predicting the development of severe anaemia during TVR-based triple therapy.^[16] Even though we practice in a rapidly changing environment because of the introduction of next generation of direct acting anti-virals (DAAs) and the potential use of IFN-free regimens in the near future,^[17, 18] little detailed data related to the virological efficacy of treatment with DAAs for advanced fibrosis patients have been reported in clinical practice.

The aims of this prospective, multicentre study were to evaluate the efficacy and safety of TVR-based triple therapy for chronic hepatitis C genotype 1 patients with advanced fibrosis. We attempted to determine if interleukin 28B (IL28B) single nucleoside polymorphisms (SNPs), adverse effects, and treatment adherence were related to the treatment outcome of patients with advanced fibrosis.

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Patients

The Kyushu University Liver Disease Study (KULDS) Group consists of Kyushu University Hospital and its affiliated hospitals in the northern Kyushu area of Japan. This prospective study consisted of 102 Japanese patients with chronic HCV infection and advanced fibrosis (METAVIR score F3–4) aged 20 years or older who received TVR in combination with PEG-IFN α 2b and RBV. All initiated treatment between December 2011 and June 2012 and was completed by the end of December 2012. Exclusion criteria were as follows: (i) positivity for antibody to human immunodeficiency virus or positivity for hepatitis B surface antigen; (ii) clinical or biochemical evidence of hepatic decompensation (Child-Pugh

B or C, ascites, bleeding varices, or encephalopathy); (iii) other causes of liver disease (haemochromatosis, autoimmune hepatitis, or primary biliary cirrhosis); (iv) excessive active alcohol consumption (a daily intake of more than 40 g of ethanol), drug abuse or severe mental disorder; (v) the presence of active cancer at entry; or (vi) treatment with anti-viral or immunosuppressive agents prior to enrolment. This clinical study had no upper age limit and put no restrictions on blood cell count, which reflects the setting of day-to-day clinical practice. Of the 185 treatment-experienced patients with chronic HCV genotype 1b infection and advanced fibrosis screened, 106 (57.3%) were excluded because they meet the exclusion criteria, mainly hepatic decompensation or the presence of hepatocellular carcinoma. In addition, some patients rejected TVR-based treatment due to very old age. The baseline characteristics of the 102 studied patients are shown in [Table 1](#). This study consisted of comparatively elderly patients (median age; 62 years), 77.5% (79 of 102) of whom were treatment-experienced patients.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of each participating hospital. Informed consent was obtained from all patients before enrolment. This study was registered as clinical study on the University Hospital Medical Information Network (ID 000011105).

Clinical and Laboratory Assessment

Clinical parameters were measured by standard laboratory techniques at a commercial laboratory (SRL Laboratory, Tokyo, Japan). Body mass index was calculated as weight in kilograms/height in square metres. The estimated glomerular filtration rate (eGFR) was calculated based on the Modification of Diet

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in Renal Disease (MDRD) formula.

Human genomic DNA was extracted from peripheral blood. Genotyping of the IL28B (rs8099917)^[19–21] and ITPA (rs1127354)^[16, 22] genes was performed using the ABI TaqMan allelic discrimination kit (7500 Real Time PCR System; Applied Biosystems, Carlsbad, CA, USA). The IL28B and ITPA SNPs data were available for 96 (94.1%) of the 102 participants.

Assessment of Liver Fibrosis

Liver biopsy for all studied patients was done by experienced hepatologists. All anti-viral treatment was initiated within 6 months after liver biopsy. The minimum length of the liver biopsy was 15 mm and at least 10 complete portal tracts were necessary for inclusion. For each specimen, the stage of fibrosis was established according to the METAVIR score.^[23]

Anti-viral Treatment

All patients received a combination treatment of TVR (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan), PEG-IFN α 2b (PEG-Intron; MSD, Tokyo, Japan), and RBV (Rebetol; MSD) for 12 weeks, followed by an additional 12 weeks of PEG-IFN α 2b and RBV alone. TVR 750 mg was administered three times a day at an 8 h interval after each meal. PEG-IFN α 2b was injected subcutaneously once weekly at a dose of 1.5 μ g/kg. RBV was given orally at a daily dose of 600–1000 mg based on body weight (600 mg for patients weighing <60 kg, 800 mg for those weighing 60–80 kg, and 1000 mg for those weighing >80 kg). The above durations and dosages are those approved by the Japanese Ministry of Health, Labor, and Welfare. If marked anorexia, an elevation of serum creatinine, or severe anaemia developed, the TVR dose could be reduced to 1500 mg/day, as previously reported.^[16] Erythropoietin use was not allowed during treatment, but blood transfusion was allowed when necessary.

For patients with grade 1 (localised to one or several sites) or 2 (diffuse skin eruption involving up to 50% of the body surface) dermatological disorders, medical management was performed at the discretion of the physicians at each hospital. If a progressive grade 3 dermatological disorder developed (involving more than 50% of the body surface, or rash with the appearance of substantial systemic signs or symptoms), TVR was discontinued but the patients continued to receive PEG-IFN α 2b and RBV. All treatment was discontinued by patients with a less than 2 log₁₀ HCV RNA decrease from baseline to week 12.

HCV RNA Level and HCV Genotype

Clinical follow-up of HCV viraemia was done by real-time reverse transcriptase PCR assay (COBAS® TaqMan® HCV assay; Roche Diagnostics, Tokyo, Japan), with a lower limit of quantification of 15 IU/mL and an outer limit of quantification of 6.9×10^7 IU/mL (1.2–7.8 log IU/mL referred to log₁₀ IU/mL).^[24] HCV RNA levels were measured at baseline, regularly during treatment, at early discontinuation, and at follow-up visits after the end of treatment. HCV genotype determination was by sequence determination in the 5'-non structural region of the HCV genome followed by phylogenetic analysis.^[25]

Previous virological response to PEG-IFN α and RBV treatment was categorised as follows: Prior relapse, undetectable HCV RNA at the end of treatment but detectable HCV RNA within 24 weeks after the end of treatment and the re-appearance of HCV RNA at any time during treatment after virological response (breakthrough). Prior partial response, a more than 2 log IU/mL decrease in the HCV RNA level from baseline at week 12 but detectable HCV RNA at weeks 12 and 24. Prior null response, a decrease in the HCV RNA level of less than 2 log IU/mL at week 12. Virological response was categorised as follows: Rapid virological response (RVR), undetectable HCV RNA at week 4. SVR, undetectable HCV RNA at week 24 after the end of treatment.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics 19.0 (IBM SPSS Inc, Chicago, IL, USA). Baseline continuous data are expressed as median (first-third quartiles) and categorical variables are reported as frequencies and percentages. Univariate analyses were done using the Chi-squared, Fisher's Exact, Mann–Whitney *U*-tests, or analysis of variance (anova) as appropriate. Variables with $P < 0.05$ in univariate analysis were used in multivariate logistic regression analysis to identify variables significantly associated with treatment outcome. The results are expressed as odds ratios (OR) and their 95% confidence interval (CI). The significance of trends in values was determined with the Cochran–Armitage trend test. A *P* value less than 0.05 was regarded as statistically significant in all analyses.



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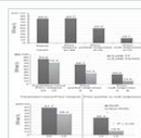
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Results

SVR Rates of the Patients with Advanced Fibrosis

The SVR rate of the patients with advanced fibrosis was 69.6% (71 of 102). However, for treatment-naïve and prior relapse patients, a high SVR rate (over 80%) was found. The SVR rate was significantly low, decreasing to 50.0% and 16.7% for patients with prior partial and null response respectively (Figure 1A).



(Enlarge Image)

Figure 1.

The sustained virological response (SVR) rates by telaprevir-based triple therapy. (a) The SVR rates stratified by previous treatment outcome. (b) The SVR rates stratified by previous treatment outcome and IL28B allele (rs8099917). (c) The SVR rates stratified by previous treatment outcome and rapid virological response (RVR, undetectable HCV RNA at week 4).

Regardless of previous treatment outcome, the SVR rates of patients with the IL28B TG/GG genotype and non-RVR were generally lower than those of patients with the IL28B TT genotype and RVR respectively. For patients with prior null response and the IL28B TG/GG genotype, the SVR rate was exceptionally low at 12.5% (Figure 1B). The SVR rate of prior partial or null responders who obtained RVR was significantly higher than that of those with non-RVR. The SVR rate of prior partial or null response/non-RVR patients was only 14.3% (Figure 1C).

Predictors of SVR by Patients with Advanced Fibrosis (Table 2)

Univariate analysis of baseline predictors of SVR of patients with advanced fibrosis identified male ($P = 0.0349$), higher platelet count ($P = 0.0028$), IL28B TT genotype ($P = 0.0034$), and treatment-naïve/prior relapse ($P < 0.0001$) as being associated with SVR. In the analysis of on-treatment predictors of SVR, the mean dosage of PEG-IFN α 2b or RBV and RVR were strongly associated with SVR ($P = 0.0088$, $P = 0.0438$ and $P = 0.0003$ respectively). However, the mean weight-adjusted dosage of TVR did not impact the treatment outcome. Multivariate logistic regression analysis of the data of advanced fibrosis patients extracted treatment-naïve/prior relapse (OR 6.14, 95% CI 1.97–20.61, $P = 0.0022$), RVR (OR 5.73, 95% CI 1.91–19.08, $P = 0.0026$), and IL28B TT genotype (OR 3.17, 95% CI 1.05–10.65, $P = 0.0438$) as being independently associated with SVR.

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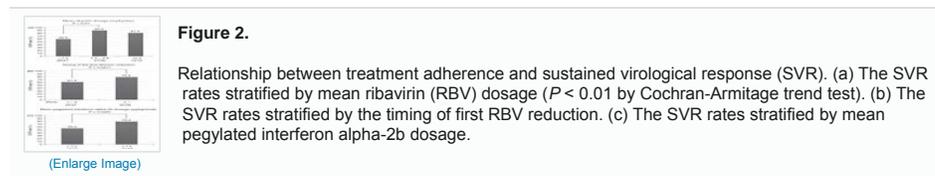
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Association between the Mean PEG-IFN α 2b or RBV Dosages and Treatment Outcome

The adherence analysis included 93 patients (91.2%) after the exclusion of nine who discontinued in the first 12 weeks. Almost all patients (92.5%, 86 of 93) required RBV reduction, mainly due to haemolytic anaemia. The SVR rates for the mean RBV dosage 7.5–9.9 mg/kg/day and ≥ 10.0 mg/kg/day groups were similar, 90.0% and 81.2% respectively. However, the SVR rate for the mean RBV dosage < 7.5 mg/kg/day group (59.6%, 28 of 47) was significantly lower than that of the ≥ 7.5 mg/kg/day group ($P < 0.05$) (Figure 2A). Furthermore, patients who required RBV reduction in the early stages of treatment (by week five) had a decreased SVR rate, but without statistical significance (Figure 2B).

Table 2



On the other hand, most patients (73.1%, 68 of 93) adhered to $\geq 80\%$ (1.2 $\mu\text{g}/\text{kg}/\text{week}$) of the assigned PEG-IFN α 2b dosage. The SVR rate for the mean PEG-IFN α 2b dosage ≥ 1.2 $\mu\text{g}/\text{kg}/\text{week}$ group was significantly higher than of the < 1.2 $\mu\text{g}/\text{kg}/\text{week}$ group (79.4% and 56.0% respectively) (Figure 2C).

Adverse Effects and Discontinuation of Treatment by Patients with Advanced Fibrosis

Serious adverse effects are shown in Table 3. About half of the patients with advanced fibrosis experienced severe anaemia [haemoglobin (Hb) < 85 g/L]. Univariate analysis extracted lower eGFR ($P = 0.0363$), lower baseline Hb level ($P = 0.0001$) and ITPA CC (rs1127354) ($P = 0.0008$) as significantly associated with the development of severe anaemia during treatment. Multivariable logistic regression analysis of predictors of the development of severe anaemia extracted baseline Hb < 135 g/L (OR, 3.09; 95% CI, 1.28–7.79; $P = 0.0122$) and ITPA CC genotype (OR, 6.36; 95% CI, 1.83–29.87; $P = 0.0027$) as significant. Of the other haematological adverse effects, 22.5% of the patients experienced neutropaenia and 15.7% had thrombocytopaenia of grade 3. Treatment with TVR was associated with the development of a dermatological disorder by 33.4%. There was only one patient (1.0%) with development of hepatic encephalopathy, but none mortally.

Infections requiring antibiotic treatment (excluding upper respiratory infections which were presumed to be viral) were experienced by 6.9% ($n = 7$) of patients with advanced fibrosis. In univariate analysis, only pre-treatment serum albumin (< 35 g/L; OR 6.11, 95% CI 1.75–19.28, $P = 0.0062$) was associated with the onset of infection; age, gender, fibrosis stage, neutropaenia, diabetes mellitus and the use of a systemic corticosteroid for a dermatological disorder were not. Of the infections, 42.9% (3 of 7) were urinary tract infection, including pyelonephritis and prostatitis. In addition, 71.4% (5 of 7) of the infections occurred within 8 weeks after the initiation of treatment. All were able to continue anti-viral treatment in combination with antibiotic treatment.

Treatment discontinuation was observed in 20 patients (19.6%). However, the rate of discontinuation due to adverse effects was decreased to 12.7% ($n = 13$) with this therapy. The reasons for premature discontinuation due to adverse effects were as follows: marked anorexia/fatigue ($n = 6$), acute kidney injury by TVR ($n = 2$), the onset of auto-immune disease ($n = 2$), severe anaemia ($n = 1$), interstitial pneumonia ($n = 1$) and malignant lymphoma ($n = 1$). Among the seven patients who discontinued treatment for non-adverse effects, six (85.7%) discontinued because of virological failure (five with viral breakthrough between weeks 16 and 20 and one with non virological response in the first 12 weeks).

Analyses According to the Serum Albumin Level (35 g/L) and Platelet Count ($100 \times 10^9/\text{L}$) by Advanced Fibrosis Status

The patients were divided into four groups according to platelet count (< 100 and $\geq 100 \times 10^9/\text{L}$) and serum albumin (< 35 and ≥ 35 g/L) to further evaluate the rates of discontinuation due to adverse effects, the onset of severe infections, and SVR, as shown in Table 4. The rates of discontinuation due to adverse effects were not associated with serum albumin or platelet count, however, severe infections were developed more often by patients with serum albumin < 35 g/L (16.0%, 4 of 25) compared with ≥ 35 g/L (3.9%, 3 of 77) ($P = 0.0551$), and the SVR rate of patients with a platelet count $\geq 100 \times 10^9/\text{L}$ (75.7%, 53 of 70) was higher than that of patients with $< 100 \times 10^9/\text{L}$ (56.3%, 18 of 32) ($P = 0.0507$).



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Discussion

This prospective, multicentre study was carried out to assess the efficacy and safety of TVR-based triple therapy for advanced fibrosis (F3–4) patients infected with HCV genotype 1b. The SVR rate of patients with advanced fibrosis was relatively low compared to patients with no or mild fibrosis (F0–2),^[11, 12] however, advanced fibrosis patients with prior relapse and IL28B TT genotype (rs8099917) achieved SVR at a rate of over 80%. In multivariate logistic regression analysis, previous treatment response, IL28B SNPs and RVR were strongly associated with treatment outcome. Blood cytopaenia and dermatological disorders were the most frequent serious adverse effects; notably, severe anaemia and infections were related to the ITPA SNPs (rs1127354) and serum albumin <35

g/L respectively.

According to recent reports on clinical trials of TVR-based triple therapy, prior partial/null response patients with advanced fibrosis had lower SVR rates than those without advanced fibrosis, although the SVR was higher than by the dual therapy.^[11, 12] A strong point of this study is that the important factors affecting treatment outcome, including treatment adherence and IL28B SNPs were investigated. Moreover, over half of our studied patients were over 60 years and we recently confirmed the effectiveness and safety of TVR-based triple therapy for older patients.^[26] One of the major findings of this study is that the SVR rate of prior null response/IL28B TG/GG genotype patients with advanced fibrosis was extremely low (12.5%) when compared to the rates of the other groups studied, despite there being no significant difference in pre-treatment parameters. Moreover, RVR is critical to the prediction of SVR, especially for patients with prior partial/null response.

Adherence to the therapeutic regimens affects the efficacy of PEG-IFN α and RBV treatment. Gordon *et al.* reported a relationship between treatment adherence and SVR in boceprevir-based therapy,^[27] however, adherence data for TVR-based therapy have not as yet been adequately analysed. Although we recently showed that the TVR plasma trough concentration in the early stage of treatment is associated with treatment outcome, even if there is advanced fibrosis,^[28] the mean weight-adjusted TVR dosage had little impact on treatment outcome in this study. On the other hand, an adequate dosage of PEG-IFN α 2b and RBV is necessary for patients with advanced fibrosis to achieve SVR.

Of the various adverse effects, the development of severe anaemia is one of the most serious problems with TVR-based triple therapy: Almost all (92.5%, 86 of 93) of the patients needed RBV dose reduction.

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In this study, lower baseline Hb level and ITPA CC (rs1127354) genotype were independently associated with the development of severe anaemia, as in our recent report.^[16] The Japanese profile of chronic hepatitis C is characterised by a large number of patients of older age and with lower BMI in comparison with European and American profiles. Because of this, TVR reduction (1500 mg/day) is allowed instead of TVR discontinuation in Japan when severe anaemia occurs. In fact, TVR adherence had little impact on treatment outcome, as stated above.

No significant differences in the discontinuation rate due to adverse effects were found when the advanced fibrosis group was stratified by platelet count ($100 \times 10^9/L$) and serum albumin (35 g/L), although a severe haematological disorder (neutropenia and thrombocytopenia) was frequently found. According to the CUPIC study, deaths and severe complications, such as severe infections and hepatic decompensation, were related to lower platelet count ($<100 \times 10^9/L$) and lower serum albumin level (<35 g/L).^[15] Fortunately, none of the patients in this study died, partly due to the exclusion of patients with Child-Pugh B or C at entry, but low serum albumin (<35 g/L) was associated with severe infections. For patients with treatment-naïve and prior relapse, adequate treatment success can be expected, even in the case of advanced fibrosis with low platelet count and low serum albumin level; therefore, TVR-based triple therapy should be decided considering the risk of severe complications, to prevent HCV-related mortality from the early period.^[29]

The recommended treatment duration of TVR-based triple therapy for cirrhotic patients is 48 weeks (24 weeks of PEG-IFN α and RBV added to standard 24 week regimen) even if RVR is obtained,^[30, 31] although the clinical evidence is insufficient to be conclusive.^[32] However, all of our studied patients received the standard triple therapy regimen (24 weeks). Almost all Japanese HCV patients are infected with genotype 1b, 2a, or 2b, rarely genotype 1a. On-treatment virological failure and the emergence of resistance to TVR are less frequent with genotype 1b than 1a because of nucleotide differences in the genetic barrier at position R155K in HCV.^[33] Moreover, this study consisted mostly of older patients; thus, although prolonged treatment may increase the chance of SVR, it also raises treatment-related safety concerns that can eventually affect the patients' health-related quality of life.^[34] However, it is generally agreed that the difference in the duration of treatment after the end of TVR administration can influence treatment outcome; therefore, further studies of patients with advanced fibrosis will be necessary to clarify the anti-viral effects and safety in other ethnic groups and patients with prolonged PEG-IFN α and RBV.

In summary, treatment success by TVR-based triple therapy for chronic hepatitis C patients with advanced fibrosis is highly expected for those with treatment-naïve and prior relapse; moreover, IL28B SNPs (rs8099917) and RVR are of great help in the prediction of SVR. Although patients with advanced fibrosis are at higher risk for blood cytopenia, the ITPA SNPs (rs1127354) was useful for predicting severe anaemia. In addition, lower serum albumin level (<35 g/L) was associated with the occurrence of severe infections. New DAAs will be available in the near future, thus the development of novel treatment strategies for prior null response and IL28B TG/GG genotype patients are of great importance.

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EO drafted the manuscript and contributed to statistical analysis. NF and JF critically revised the manuscript for important intellectual content. All authors collected the data, contributed to the design of the study and approved the final version of the manuscript.

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