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ORIGINAL PAPER

# High total bilirubin level is a significant risk factor for severe neutropenia in patients receiving irinotecan-based chemotherapy

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## Abstract

Irinotecan is effective for the treatment of metastatic colorectal cancer (mCRC) and advanced pancreatic cancer (aPC). However, these treatments are often limited due to the incidence of severe neutropenia. We identified risk factors for severe neutropenia in patients with mCRC or aPC, receiving irinotecan-based chemotherapy regimens. The study selected 104 patients (mCRC: 53 and aPC: 51) who received irinotecan-based chemotherapy between January 2014 and May 2018 and who were included in the present study. The initial dose of irinotecan was 150 mg/m$^2$ in all patients, and patients with a lower initial dose of irinotecan were excluded. Severe neutropenia (grade ≥ 3) occurred in 56 patients (53.8%). Multivariable Cox proportional hazards analysis indicated that modified FOLFIRINOX (mFOLFIRINOX) and serum total bilirubin (T-Bil) were significant risk factors for severe neutropenia. Moreover, with receiver-operating characteristic (ROC) curve analysis, the cutoff for T-Bil was found to be 0.7 mg/dL. Among patients treated with mFOLFIRINOX therapy, the incidence of severe neutropenia was significantly higher in patients with high level of T-Bil (> 0.7 mg/dL) than in those without it (93.8% vs 55.0%, $P = 0.006$). A chemotherapy regimen (modified FOLFIRINOX therapy) and T-Bil > 0.7 mg/dL were significant risk factors for severe neutropenia in patients receiving 150 mg/m$^2$ irinotecan.

**Keywords** Irinotecan · Severe neutropenia · High level of total bilirubin · Modified FOLFIRINOX · Metastatic colorectal cancer · Advanced pancreatic cancer

## Introduction

Irinotecan, a topoisomerase I inhibitor, is effective for the treatment of metastatic colorectal cancer (mCRC) as a monotherapy [1] or in combination with fluoropyrimidines [2, 3] in the absence or presence of monoclonal antibodies raised against vascular endothelial growth factor or the epidermal growth factor receptor [4, 5]. In addition, this agent is effective for prolonging the survival of patients with advanced pancreatic cancer (aPC) when used in combination with oxaliplatin and fluoropyrimidines (FOLFIRINOX regimen) [6]. To reduce the incidence of toxicities associated with FOLFIRINOX, the chemotherapy regimen has been modified by omitting the bolus injection of 5-fluorouracil and/or reducing the dose of irinotecan without reducing the clinical response, which is known as modified FOLFIRINOX (mFOLFIRINOX) [7, 8].

Irinotecan is metabolized by carboxylesterase in the human liver to form the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), which in turn is inactivated by glucuronidation by UDP-glucuronyltransferase (UGT) 1A1 to yield SN-38 glucuronide (SN-38G), which has no pharmacological or toxic actions [9, 10]. Polymorphisms in the UGT1A1 gene are associated with irinotecan-induced adverse events. Patients with homozygous

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mutations of the UGT1A1 gene (*28/*28, *6/*6 and *28/*6) experience severe neutropenia more frequently than those with the wild-type allele [11–16]. Therefore, dose reduction of irinotecan based on UGT1A1 genetic polymorphisms is recommended to prevent severe adverse events. Nevertheless, severe neutropenia still occurs in patients without homozygous mutations of the UGT1A1 gene [14, 15], suggesting that there are other factors that affect the incidence of severe neutropenia associated with irinotecan.

We previously reported that the incidence rate of neutropenia (grade ≥ 3) was 42.9% and 25.0% in mCRC patients with heterozygous mutations and the wild-type allele for the UGT1A1 gene, respectively, after treatment with 150 mg/m$^2$ irinotecan [15]. Our previous data were generally consistent with those reported by Ichikawa et al. [17], who showed that the incidence rates of grade 3 or 4 neutropenia were 34.1% and 25.2% in mCRC patients with heterozygous mutations and the wild-type allele, respectively.

Serum total bilirubin (T-Bil) is one laboratory biomarker used to predict hepatobiliary disease. Evidence suggests that the area under the plasma drug concentration–time curve (AUC) of SN-38 is closely associated with serum levels of T-Bil [18].

Here, we investigated factors that affect the incidence of severe neutropenia in patients without homozygous mutations of the UGT1A1 gene receiving irinotecan-based chemotherapy for mCRC or aPC.

## Patients and methods

### Patients

A total of 155 patients with mCRC or aPC received irinotecan-based chemotherapy in our outpatient chemotherapy clinic between January 2014 and May 2018. Of these, 51 patients were excluded from our study: initial dose of irinotecan was reduced in 13 patients because of poor general status due to aging, myelosuppression occurred in 10 patients, performance status was low in 9 patients (> 2 according to the Eastern Cooperative Oncology Group), homozygous mutations in the UGT1A1 gene such as UGT1A1*28/*28, UGT1A1*6/*6, and UGT1A1*28/*6 were detected in 12 patients, and therapy duration was less than three cycles in 7 patients. The initial dose of irinotecan was 150 mg/m$^2$ in all eligible patients. Therefore, data from the remaining 104 patients were analyzed in the present study. Data were obtained from electronic medical records in our hospital and analyzed retrospectively. In our laboratory, the upper limit of normal for T-Bil is 1.2 mg/dL.

### Assessment of adverse events

Irinotecan-induced adverse events, including neutropenia, leukopenia, thrombocytopenia, and febrile neutropenia (FN), were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

### Risk analysis for severe neutropenia

Heterozygous mutations of the UGT1A1 gene such as UGT1A1*6/*1 or UGT1A1*28/*1, low neutrophil count, smoking history, and high T-Bil levels are reported risk factors for severe neutropenia in patients receiving irinotecan-based chemotherapy [19–21]. FOLFIRINOX therapy is a triplet regimen consisting of irinotecan, oxaliplatin, and 5-fluorouracil, and the incidence of neutropenia reported following treatment with FOLFIRINOX is high compared with that resulting from FOLFIRI [2–4, 7, 8].

The presence of both biliary stent and drainage was included in the risk analysis because these may affect the enterohepatic circulation of irinotecan. In addition, age and sex were included in the analysis as adjustment factors.

### Statistical analysis

Data were analyzed using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan), GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA), and R software version 3.5.1 (www.r-project.org). *P* values less than 0.05 were considered significant. Patient demographics were summarized using medians with 25th and 75th percentiles for parametric variables. Frequencies and percentages are shown for non-parametric variables.

Risk factors for severe neutropenia were assessed using the multivariable Cox proportional hazards model adjusted for covariates, and hazard ratios (HRs) and 95% confidence intervals (CIs) were determined. Explanatory variables were restricted to six items, T-Bil, mFOLFIRINOX regimen, UGT1A1 polymorphisms, smoking history, number of neutrophils, and biliary stent or drainage, and two covariates (age and sex) to avoid overfitting. Nonlinear associations between neutropenia and T-Bil were assessed using restricted cubic splines in a regression model. The reliability of the Cox regression model was internally validated using the bootstrap method by measuring overfitting quantified with the optimism parameter from a calibration plot. One hundred and fifty resamples were performed with bootstrap with replacement. An optimism value less than 0.2 indicated no evidence of overfitting. Variance inflation factors (VIFs) were used to determine the degree of co-linearity, with a value < 2 indicating no evidence of co-linearity. The

incidence of severe neutropenia was compared between patients whose T-Bil levels were lower and higher than the cutoff value using the Chi-squared test. The cutoff value for T-Bil was determined using the Youden index method [22] in the receiver operating characteristic curve (ROC) with 10,000 sets of bootstrap resamples.

### Ethics statement

The present study was conducted in accordance with the guidelines for human studies adopted by the ethics committee of Gifu University Graduate School of Medicine and notified by the Japanese government (Institutional review board approval No. 2018-220). Due to the retrospective nature of the study, the need for informed consent from subjects was not mandated. All procedures in the present study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Results

### Patients

A total of 104 patients were analyzed in the present study as shown in Table 1. Among them, 63 (60.6%) were male and 41 (39.4%) were female, and the median age was 64.5 years. Forty (38.5%) patients harbored a heterozygous mutation in the UGT1A1 gene such as UGT1A1*28/*1 or UGT1A1*6/*1. Fifty-one patients with aPC received mFOLFIRINOX therapy, and 53 patients with mCRC received irinotecan monotherapy ($N=5$), or a FOLFIRI-based ($N=37$) or IRIS-based regimen ($N=11$). The initial dose of irinotecan was 150 mg/m$^2$ biweekly in all patients. Biliary stent or drainage was only conducted in patients with aPC ($N=15$, 14.4%).

### Incidence of grades of irinotecan-induced adverse events

Irinotecan-induced adverse events were graded during all courses of chemotherapy. Incidence rates of grade ≥2 and grade ≥3 neutropenia were 68.3% and 53.8%, respectively. FN (grade 3) developed in 9.6% of patients. Incidence rates of grade 1 and grade ≥2 thrombocytopenia were 39.4% and 14.4%, respectively (Table 2).

### Risk factors for severe neutropenia

Figure 1 shows that there was a weak nonlinear relationship between T-Bil and the predicted probability of severe neutropenia ($P=0.047$). As shown in Table 3, mFOLFIRINOX therapy and high levels of T-Bil were significant independent risk factors for severe neutropenia (mFOLFIRINOX therapy: HR 4.11, 95% CI 2.15–7.86, $P<0.001$; T-Bil: HR 1.85, 95% CI 1.23–2.78, $P=0.004$). The Cox regression model was internally validated, and the estimated optimism was 0.191, indicating that there was no evidence of overfitting. The VIF did not exceed 2 for any

**Table 1** Patient demographics

| Number of patients (male/female) | 104 | (63/41) |
|---|---|---|
| Age, median (min–max) | 64.5 | (42–82) |
| Allele frequency for UGT1A1*6 and UGT1A1*28, *N* (%) | | |
| UGT1A1*6/*1 | 22 | 21.2% |
| UGT1A1*28/*1 | 18 | 17.3% |
| Wild-type | 64 | 61.5% |
| Height (cm) | 162 | (156–166.4) |
| Body weight (kg) | 56 | (49–61.8) |
| Aspartate aminotransferase (IU/L) | 22.5 | (18–33.3) |
| Alanine aminotransferase (IU/L) | 18 | (13–28.3) |
| Serum creatinine (mg/dL) | 0.69 | (0.55–0.82) |
| Total bilirubin (mg/dL) | 0.7 | (0.58–0.8) |
| Neutrophils (/L) | 3260 | (2580–4252.5) |
| White blood cells (/L) | 5390 | (4535–6375) |
| Hemoglobin (g/dL) | 12.5 | (11.3–13.4) |
| Platelets ($10^4$/L) | 19.2 | (15.8–24.4) |
| Cancer, *N* (%) | | |
| Colorectal cancer | 53 | 51.0% |
| Pancreatic cancer | 51 | 49.0% |
| Regimen, *N* (%) | | |
| Irinotecan monotherapy | 5 | 4.8% |
| FOLFIRI | 37 | 35.5% |
| IRIS | 11 | 10.6% |
| Modified FOLFIRINOX | 51 | 49.0% |
| With smoking history, *N* (%) | 52 | 50.0% |
| With biliary stent or drainage, *N* (%) | 15 | 14.4% |

All data indicate median (25–75th percentiles) unless otherwise indicated

**Table 2** Incidence rates of hematological adverse events and febrile neutropenia

| | Neutropenia (%) | Leukopenia (%) | Thrombocytopenia (%) | Febrile neutropenia (%) |
|---|---|---|---|---|
| Grade 1 | 0.0 | 6.7 | 39.4 | 0.0 |
| Grade 2 | 14.4 | 37.5 | 12.5 | 0.0 |
| Grade 3 | 31.7 | 20.2 | 1.9 | 9.6 |
| Grade 4 | 22.1 | 4.8 | 0.0 | 0.0 |
| Grade ≥ 2 | 68.3 | 62.5 | 14.4 | 0.0 |
| Grade ≥ 3 | 53.8 | 25.0 | 1.9 | 9.6 |

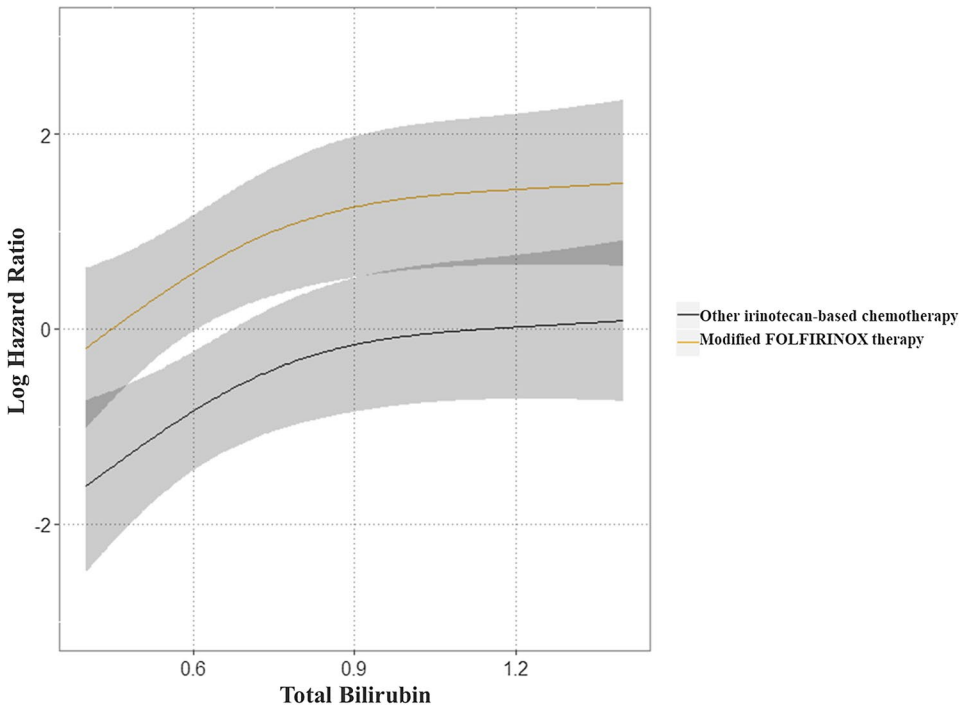


**Fig. 1** Log-relative hazards for severe neutropenia and total bilirubin using restricted cubic splines in a regression model in patients receiving irinotecan-based chemotherapy

**Table 3** Cox proportional hazards analysis of the risk of grade ≥ 3 neutropenia in patients receiving irinotecan-based chemotherapy

| Factor | HR | 95% CI | | *P* value |
|---|---|---|---|---|
| Modified FOLFIRINOX therapy | 4.11 | 2.15 | 7.86 | < 0.001 |
| Heterozygous for UGT1A1*6 or *28 | 1.34 | 0.75 | 2.40 | 0.322 |
| Low neutrophil count | 0.77 | 0.49 | 1.19 | 0.239 |
| With smoking history | 0.70 | 0.36 | 1.33 | 0.272 |
| With biliary stent or drainage | 0.92 | 0.45 | 1.87 | 0.806 |
| Total bilirubin | 1.85 | 1.23 | 2.78 | 0.004 |

Hazard ratios (HRs) and 95% confidence intervals (CIs) are indicated. Analysis was performed with adjustment for age and sex

variable, indicating that there was no evidence of substantial co-linearity.

### Comparison of the incidence rates of severe neutropenia between patients with high (≥ 0.7 mg/dL) and low (< 0.7 mg/dL) T-Bil levels

According to ROC analysis, the cutoff value for T-Bil in all patients was 0.7 mg/dL. The AUC for T-Bil was 0.676 (95% CI 0.574–0.778). Among patients who received mFOLFIRINOX therapy, severe neutropenia occurred significantly more frequently among those with high T-Bil (≥ 0.7 mg/dL) than among those with low (< 0.7 mg/dL) T-Bil (90.3% vs 55.0%, $P < 0.01$; Fig. 2). Similarly, among patients who received irinotecan-based chemotherapy regimens other than mFOLFIRINOX therapy, the incidence of severe neutropenia was higher among patients with T-Bil ≥ 0.7 mg/dL than those with T-Bil < 0.7 mg/dL, although the difference was not significant (41.9% vs 18.2%, $P = 0.082$; Fig. 2). The incidences of FN were tended to be slightly higher among patients with T-Bil ≥ 0.7 mg/dL than those with T-Bil < 0.7 mg/dL in patients who received mFOLFIRINOX therapy (19.4% vs 10.0%, $P = 0.456$) or other irinotecan-based chemotherapy regimens (6.5% vs 0%, $P = 0.505$).

## Discussion

While irinotecan-based chemotherapy is effective for the treatment of various types of cancers, it is also associated with the risk of severe neutropenia [1–8]. Several reports have shown that irinotecan-induced adverse events are associated with a decrease in glucuronidation of UGT1A1 [11–17], suggesting that dose adjustment of irinotecan should be recommended based on UGT1A1 genetic polymorphisms [14, 15]. In the present study, risk factors other than homozygous mutations of the UGT1A1 gene for severe neutropenia were explored in patients with mCRC or aPC receiving irinotecan-based chemotherapy regimens.

In the present study, 56 of 104 patients (53.8%) experienced severe (grade ≥ 3) neutropenia. Ichikawa et al. [17] reported incidence rates of 25.2% and 34.1% for grade 3 or 4 neutropenia in mCRC patients with wild-type and heterozygous mutations of the UGT1A1 gene, respectively, after treatment with irinotecan-based chemotherapy regimens. In our study, the incidence of severe neutropenia was 32.1%

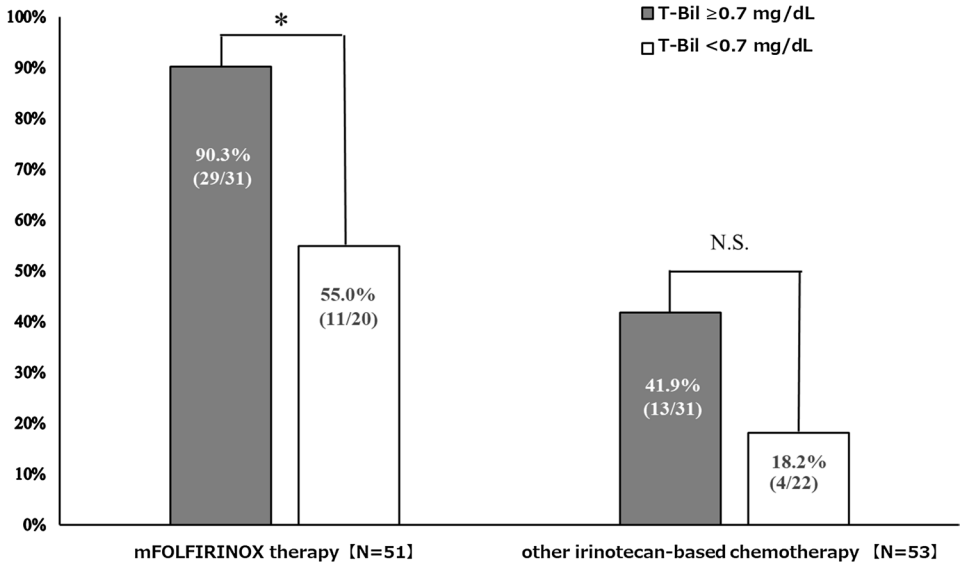


**Fig. 2** Comparison of the incidence rates of severe neutropenia between patients with total bilirubin levels below and above the cutoff values among those receiving modified FOLFIRINOX therapy or other irinotecan-based chemotherapy. *$P < 0.01$, *N.S.* not significant

(17/53) in mCRC patients who received irinotecan-based chemotherapy regimens, which is consistent with the findings reported by Ichikawa et al. [17]. In contrast, Yoshida et al. [7] reported that the incidence of grade ≥ 3 neutropenia was 83.9% in aPC patients receiving mFOLFIRINOX therapy in a phase II study. Consistent with their data, we found that severe neutropenia appeared in 40 of 51 patients (78.4%) receiving mFOLFIRINOX therapy.

The present study identified both mFOLFIRINOX therapy and T-Bil as significant risk factors for severe neutropenia incidence associated with irinotecan. Bilirubin is a biological factor produced predominantly from the hemoglobin of senescent erythrocytes in the reticuloendothelial system in the human liver and spleen. Indirect bilirubin bound to albumin is transported to the liver and glucuronidated by bilirubin UDP glucuronosyl transferase (B-UGT). Subsequently, water-soluble direct bilirubin is excreted into bile. Raijmakers et al. [23] reported that human liver B-UGT activity is associated with a polymorphism in the promoter region of the UGT1A1 gene. Furthermore, Federico et al. [18] reported that bilirubin level is a significant covariate for the AUC of irinotecan ($P = 0.02$ to 0.05), SN-38 ($P < 0.0001$), and SN-38 G ($P = 0.04$). Additionally, Tanaka et al. [24] showed that there is a significant correlation between the AUC ratio ($AUC_{SN\text{-}38}/AUC_{SN\text{-}38G}$), which indicates the ability of SN-38 to be glucuronidated, and T-Bil before CPT-11 chemotherapy ($R^2 = 0.852$, $P < 0.0001$). Metabolism of bilirubin and SN-38 is largely affected by UGT1A1*6 and *28 polymorphisms and to a lesser extent by UGT1A1*7 [25], UGT1A1*27 [26], and UGT1A1*60 polymorphisms [11, 27]. In addition, the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene, which encodes organic anion transporting polypeptide 1B1 (OATP1B1) and exhibits genetic mutations, is also involved in the uptake of bilirubin and SN-38 into hepatocytes [28, 29]. Taken together, these findings suggest that T-Bil level and irinotecan metabolism are affected by not only the UGT1A1 activity but also by the function of several other proteins such as OATP1B1. Indeed, in the present study, elevation of T-Bil markedly increased the incidence of severe neutropenia in aPC patients who received mFOLFIRINOX therapy, and to a lesser extent in mCRC patients receiving other irinotecan-based chemotherapy regimens, suggesting that a reduction in glucuronidation activity leads to high levels of T-Bil and SN-38.

The ACCORD study [6] demonstrated that FOLFIRINOX therapy was associated with a survival advantage over gemcitabine monotherapy in aPC patients, and it has since become a standard chemotherapy. mFOLFIRINOX, a chemotherapy regimen with reduced toxicity compared to FOLFIRINOX, is also a common first-line chemotherapy in Japanese patients with aPC [7, 8]. However, the incidence of severe neutropenia was high (78.4%), particularly in patients whose T-Bil exceeded 0.7 mg/dL (90.3%). A dose reduction of irinotecan in mFOLFIRINOX therapy should therefore be recommended for aPC patients with T-Bil > 0.7 mg/dL.

## Conclusion

Severe neutropenia appeared in 53.8% of patients receiving irinotecan-based chemotherapy regimens, with the incidence being significantly higher in patients receiving mFOLFIRINOX (78.4%) compared to other irinotecan-based chemotherapy regimens. A multivariable Cox proportional hazards analysis showed that chemotherapy regimens such as mFOLFIRINOX and high T-Bil levels were significant risk factors for severe neutropenia in patients with mCRC

or aPC. ROC analysis determined that the cutoff value for T-Bil was 0.7 mg/dL.

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## Compliance with ethical standards

**Conflict of interest** K Yoshida received grants, personal fees, and non-financial support from Chugai Pharmaceutical Co., Ltd. during the conduct of this study; grants and personal fees from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., and Yakult Honsha Co., Ltd.; and grants from Bristol-Myers Squibb and Kyowa Hakko Kirin Co., Ltd. outside the submitted work. He also received honoraria from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Yakult Honsha Co., Ltd., and had a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd. and La Roche, Ltd. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to disclose.

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