

Rhabdomyolysis due to lamivudine re-administration in a patient with HBV-related hepatic failure caused by interruption of lamivudine and adefovir

To the Editor,

A 47-year-old man with chronic hepatitis B was admitted to Kobe Asahi Hospital on January 26, 2014 presenting with hepatic failure. Laboratory examinations revealed the following: total bilirubin, 3.39mg/dl; aminotransferases, AST, 2,700U/l; ALT, 1,800U/l; prothrombin time 40.8%; HBeAg(+); HBeAb(-) and HBV DNA, 9.1 log IU/ml (Real-time detection PCR test, LSI Medience Corporation, Tokyo). Under the diagnosis of chronic hepatitis B (stage F3), lamivudine (100mg once daily) had been administered since September 2004.

Liver function worsened in September 2005, and YIDD mutation was detected. IFN- α 300MU/mg three times a week was administered from October 2005 to August 2006.

In September 2006, IFN treatment was replaced by adefovir (10mg once daily). Liver function and virological markers improved steadily from April 2007 to October 2013. Laboratory examinations in June 2013 revealed the following: AST, 28U/l; ALT, 9U/l; HBeAg (-); HBeAb (-); HBV DNA was not detectable. The therapy with lamivudine and adefovir was suspended by the patient in November 2013.

On January 26, 2014 when he developed hepatic failure, administration of lamivudine and adefovir was resumed together with entecavir. On February 19, the level of creatine phosphokinase (CPK) was high (4,195 IU/l), and the levels of blood and urine myoglobin reached 648 ng/ml (normal <100 ng/ml) and 570 ng/ml (<8.5 ng/ml), respectively. Troponin T was negative and the isozyme pattern of CPK was type MM. No evidence of muscle trauma, infection, or other metabolic signs were present, and the patient demonstrated no specific symptoms. The drugs administered at the time of increased serum CPK were ursodeoxycholic acid, pitavastatin calcium, lamivudine, adefovir, and entecavir. Under the suspicion of drug-induced rhabdomyolysis, pitavastatin calcium intake was discontinued

first; however, serum CPK continued to rise, and on February 26 and 27, the level reached 18,818 IU/l and 21,633 IU/l, respectively. Next, administration of lamivudine was discontinued, leading to a continuous drop in the level of serum CPK, that reached 172 IU/l, 116 IU/l on March 7 and 14, respectively (Fig.1). From the above clinical course, lamivudine was identified as the cause of rhabdomyolysis.

Rhabdomyolysis is encountered in cases of trauma, myocardial infarction, metabolic or genetic disorders, infections, prolonged surgery, and drug administration.

Lamivudine has few adverse reactions and is very safe, especially that its adverse effects, other than induction of the YMDD-variant virus and post treatment flares, are believed to be rare [1]. In the literature, however, drug-induced rhabdomyolysis is associated with several factors, including prophylactic administration of lamivudine and treatment of HBV infection [2, 3]. Two cases of rhabdomyolysis with renal failure attributed to lamivudine administration have been reported: one in a liver transplant recipient [2], and another one of acute exacerbation

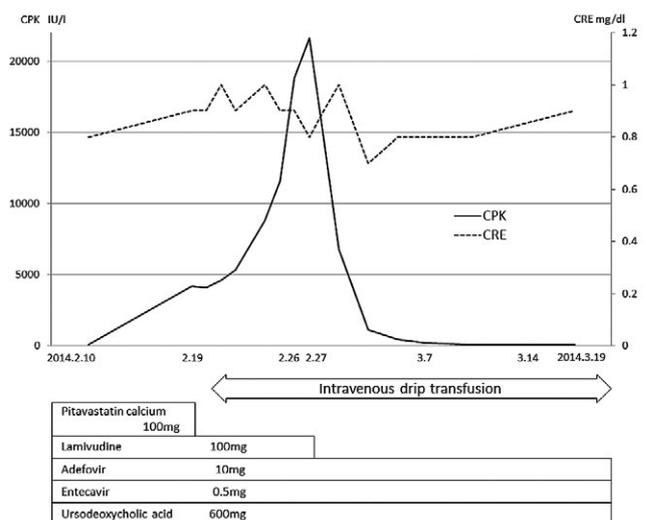


Fig. 1. Creatine phosphokinase (CPK) and creatinine (CRE) levels in our patient from February 10, 2014 to March 19, 2014.

of chronic hepatitis B [3]. In the former, even the rechallenge test and dialysis were carried out; in the latter, the patient died without undergoing dialysis. In the present case, because of intravenous drip transfusion therapy, renal function tests such as serum creatinine and azotemia were maintained within normal limits, and renal failure and dialysis were obviated.

The rechallenge test was not carried out in this patient from the viewpoint of medical ethics.

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“Learning curve“ for the POEM procedure

To the Editor,

Many recent published manuscripts have addressed the clinical efficiency of peroral endoscopic myotomy (POEM) procedure for achalasia [1-3] and some of them have focused in particular on the learning curve of this technique [3-6]. The learning process was analyzed through miscellaneous parameters (the procedure time, the accidental mucosotomies, the severe complication rate, the significant improvement of dysphagia), without standardization as it reflects a recently developed endoscopic procedure. Some studies tried to define a case number threshold for becoming an expert of the POEM procedure. In smaller case series with the main outcome defined as the procedure time, conflicting results were reported. Kurian et al. [4] reported that the mastery of the operative technique in POEM was achieved after 20 procedures and evidenced by a decrease in the length of procedure, but Teitelbaum et al. [5] concluded that the overall procedure time did not decrease with experience and may not be an important marker of procedural skill for POEM. Patel et al. [6] analyzed 93 procedures with multiple parameters that might influence

the learning curve and concluded that efficiency was attained after 40 POEMs and mastery after 60 POEMs. In this study, the adjusted regression analysis showed that the procedure time was significantly influenced by the case numbers of the operator ($p < .0001$), but the improvements in clinical outcomes were not significantly affected by operator experience. In the multicenter retrospective analysis published by Werner et al. [3], the authors analyzed the possible impact of the learning curve on POEM failures and compared the first 10 cases included on each center (30) with post-10 procedures (50) and found no significant impact of the learning curve on the cumulative rates of patients with failure ($p = 0.513$).

Our experience consists of 42 POEM procedures performed on 19 men and 23 women with a median age of 44 years (range 24-70 years) and a median for the Eckardt score of 7 (range 4-12). Mean symptom period was 30 months (range 2-100 months). Five (11.9%) patients had previous endoscopic treatment (one or two sessions of esophageal balloon dilatation), while one patient had undergone laparoscopic Heller myotomy 2 years previously. Mean lower esophageal sphincter resting pressure before treatment was 38 mmHg (range 20-70, standard deviation 16.5 mmHg). The POEM technique was performed by an expert endoscopist. All patients experienced symptom improvement immediately after the procedure. The mean myotomy length was 15 cm (range 13-18 cm). The mean number of endoscopic clips used to safely close the mucosal breach was 10 (range 5-31, standard deviation 5.8). The mean procedural time for POEM was 82 minutes (range 35-180 minutes) (with a mean of 81.85 minutes for the first 20 procedures and 82.95 minutes for the next 22 procedures). Seven (16.6%) incidents were recorded during POEM: 3 esophageal and gastric mucosal micro-perforations safely closed with clips, 1 subcutaneous emphysema and 3 instances of pneumoperitoneum, resolved with decompression using the Veress needle. No referral to surgery was needed. Post procedurally, 5 (11.1%) cases of subcutaneous emphysema associated with mild pneumoperitoneum and 15 (35.7%) cases of isolated mild pneumoperitoneum were detected and all were resolved spontaneously. No infectious or hemorrhagic complications were noted. Median hospital stay was 5 days (range 4-15 days). One month follow up depicted a significant decrease for median Eckardt scores from 7 to 0 (Wilcoxon test, $p < 0.005$). Only one patient out of 30 still experienced dysphagia at one-year follow up.

The literature data and our own experience argued that the learning process of POEM did not influence the main outcome, i.e. the dysphagia improvement. The other parameters reported such as the procedure time and the complication rate can be biased by the operators' previous experience with other difficult endoscopic procedures (mucosectomies or submucosal dissection) and complications management. Another aspect that might influence this learning process is the case management selection for POEM based on previous endoscopic experience of operators with achalasia treatment and on patients' past achalasia history.

According to our results, the learning process for POEM does not influence improvement in dysphagia and mastery might be achieved when difficult achalasia cases are resolved by this technique.

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Balloon dilatation with or without intralesional and oral corticosteroids for anastomotic Crohn's disease strictures

To the Editor,

Stricture formation is a common and challenging complication in patients with Crohn's disease (CD) leading to repeated surgery and endoscopic balloon dilatations (EBDs)[1, 2]. Although EBD is an effective bowel-conserving treatment, fifty per cent of patients will require repeated dilatations [3]. The long-term outcome of EBD may be improved by intralesional injection of corticosteroids. However, data regarding the efficacy of intralesional steroids remain conflicting [4]. Therefore, we examined whether adding intralesional triamcinolone injections and oral budesonide for 24 weeks to EBD reduces the recurrence of strictures and the need for repeat dilatation and/or surgery.

We performed a multicentre, double-blinded trial (Dutch Trial Registration no. 1378), including adult CD patients with a clinically significant symptomatic stricture of the ileocecal anastomosis who underwent routine EBD. Patients with

infectious colitis, extensive inflammation or fistulas at the site of stricture, and stricture length > 5 cm were excluded. EBD was repeated until a significant dilatation of the stricture was accomplished. Patients were randomly assigned to either four-quadrant injections of 0.5-1 mL triamcinolone (Kenacort 40 mg/mL) followed by oral budesonide for 24 weeks (tapered from 9 to 3 mg) or saline injections followed by placebo capsules. Follow-up data, including obstructive symptoms (VAS scores), clinical disease activity, and adverse events were collected at week 2, 6, 12, 24 and 52. The primary end point was the recurrence of a clinically significant stricture necessitating re-dilatation or surgery. Secondary end points were rates of clinical improvement and remission according to VAS scores. Clinical remission and clinical response were defined as a total VAS score ≤ 5 and a ≥50% decrease in total VAS score, respectively.

Nine patients (mean age 52±10 years; 33% male) were randomized, 5 to corticosteroid treatment and 4 to placebo. Groups were not significantly different with regard to baseline and stricture characteristics. In the intention-to-treat analysis, 1 out of 5 patients in the corticosteroid group required surgery and 1 out of 4 patients in the placebo group required redilatation (Cox regression $p = 0.94$, HR 0.89; 95%

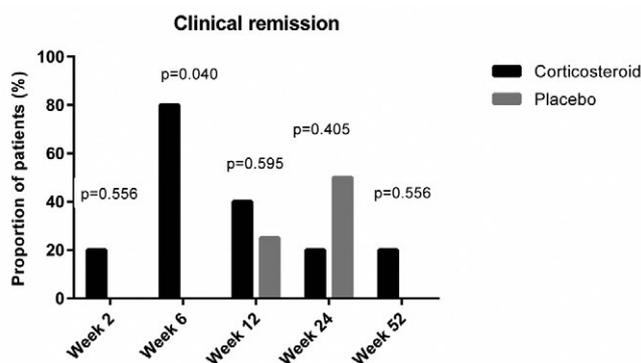


Fig. 1. Proportion of patients in clinical remission on week 2, 6, 12, 24 and 52 allocated to placebo and corticosteroid treatment. Clinical remission is defined as a total VAS score ≤ 5 of obstructive symptoms (intermittent abdominal pain, abdominal distension, nausea, vomiting and anorexia).

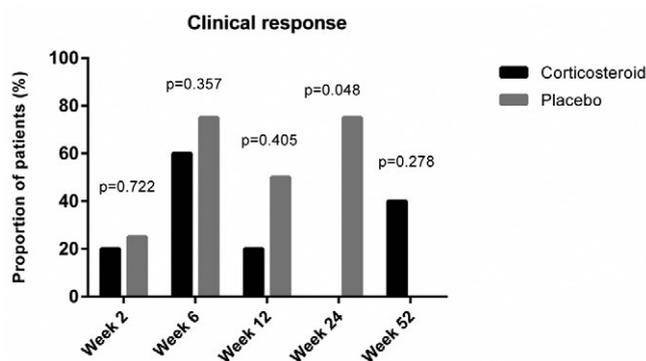


Fig. 2. Proportion of patients with clinical response on week 2, 6, 12, 24 and 52 allocated to placebo and corticosteroid treatment. Clinical response is defined as a ≥50% decrease in total VAS score of obstructive symptoms (intermittent abdominal pain, abdominal distension, nausea, vomiting and anorexia).

Table I. Baseline and stricture characteristics in our patients

Variable	All patients (n = 22)	Corticosteroid (n = 5)	Placebo (n = 4)
Age, mean (\pm SD)	46.1 (12.0)	49.1 (11.1)	56.5 (8.4)
Male, n (%)	10 (45.5)	1 (20.0)	1 (25.0)
Smoker, n (%)	7 (31.8)	1 (20.0)	1 (25.0)
Disease duration, median (IQR)	18.4 (10.9-33.8)	14.9 (9.7-38.2)	29.2 (8.4-41.0)
Montreal classification, n (%)			
L1 ileal	11 (50.0)	4 (80.0)	0 (0.0)
L3 ileocolonic	11 (50.0)	1 (20.0)	4 (100.0)
+ upper GI	1 (4.5)	0 (0.0)	0 (0.0)
B3 penetrating	3 (13.6)	1 (20.0)	0 (0.0)
+ perianal disease	5 (22.7)	1 (20.0)	0 (0.0)
Time since ileocecal resection, median (IQR), years	10.0 (4.9-25.8)	10.1 (2.1-38.1)	18.1 (0-37.9)
Current medication use, n (%)			
5-ASA	2 (9.1)	1 (20.0)	0 (0.0)
Immunomodulators	8 (36.4)	1 (20.0)	1 (25.0)
Anti-TNF agents	7 (31.8)	3 (60.0)	1 (25.0)
Disease activity, mean (\pm SD) ^a	6.7 (3.7)	7.0 (2.8)	6.3 (5.0)
C-reactive protein level, mean (\pm SD), mmol/L	3.8 (2.0)	4.2 (2.7)	3.0 (0.5)
Obstructive symptoms, mean (\pm SD)			
Abdominal pain	4.4 (2.3)	4.0 (1.8)	2.4 (2.0)
Abdominal distension	5.2 (2.6)	5.4 (2.5)	5.6 (3.7)
Nausea	3.6 (2.7)	1.3 (2.5)	6.6 (1.9)
Vomiting	1.6 (2.0)	0.2 (0.4)	2.2 (2.1)
Anorexia	3.5 (2.5)	0.8 (0.9)	3.0 (1.5)
Stricture length by MR enterography, median (IQR), cm	3.5 (1.3-5.0) ^b	2.6 (0.9-4.7)	3.3 (1.5-6.9)
Stricture length by ultrasound, median (IQR), cm	3.2 (2.0-4.2) ^c	2.9 (2.1-5.3)	3.5 (3.5-7)
Maximal balloon size, median (IQR), mm	-	18 (16-18)	18 (14-18)

^a = according to the Harvey Bradshaw Index; ^b = MR enterography available for 19 patients; ^c = abdominal ultrasound available for 18 patients

CI 0.06-14.4). Except for week 6, no difference in the rate of clinical remission was detected between the corticosteroid and placebo group at week 2 (20 vs. 0%, $p=0.556$), week 12 ($p=0.595$), week 24 (20 vs. 50%, $p=0.405$), and week 52 (20 vs. 0%, $p=0.556$) (Fig. 1). Additionally, apart from week 24, response rates were not different between the corticosteroid and placebo group (Fig. 2). No major adverse events occurred during follow-up.

In conclusion, intralesional and oral topical corticosteroids did not reduce the need for redilatation after EBD of CD ileocolonic anastomotic strictures. Several reasons may explain this negative finding. First, intralesional steroids might lead to postdilatation stricture ischemia and inflammation [5]. Second, inflammatory strictures, which may be more susceptible to treatment with corticosteroids, were not included in our study. Cautious interpretation of this negative finding is warranted, as a type II error is possible. However, considering our results and previous evidence [4, 6] we feel that intralesional

corticosteroids as an adjuvant should not be implemented into clinical practice.

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Validation of the Bristol Stool Form Scale into Romanian

To the Editor,

Data on stool form and consistency is very important when approaching patients with digestive diseases [1] or other conditions associated with changes of the bowel transit, such as endocrine diseases [2]. One of the most frequent and common functional gastrointestinal diseases is irritable bowel syndrome (IBS) [3], where the altered bowel transit represents one of the diagnostic criteria [1], thus making the assessment of bowel transit mandatory.

The most widely used and known tool for the analysis of bowel habit and stool type is the Bristol Stool Form Scale (BSFS) [4–6], with an efficacy that has been already proven in studies and in clinical practice [4, 7, 8]. To our knowledge, no translation or validation of the BSFS has been performed into Romanian, therefore we decided to translate and validate the scale into Romanian, in order to offer to healthcare and/or scientific professionals a simple and efficient tool to analyze the stools of their patients.

The study was approved by the local Ethics Committee. Permission for the translation and validation of the BSFS was authorised by the Norgine group of companies, which holds the copyright, conceded by the authors.

Translation into Romanian was performed similarly to previous validation studies: by two authorized translators, then two gastroenterologists adapted the translation, which was further translated back into English by two bilingual specialists, a physician and a native English and Romanian speaker. The final form was applied to a pilot group consisting of 12 medical professionals and 6 patients, in order to detect possible problems (see Supplementary material).

We investigated 120 healthcare professionals (30 physicians, specialists in internal medicine and/or gastroenterology, 30 medical residents, 30 nurses and 30 third-year medical students) and 60 patients, of whom 30 with IBS (14: IBS-C, 10: IBS-D, 6: IBS-M) and 30 with various other conditions recruited from the Internal Medicine and Gastroenterology Departments. The group included 54 males and 126 females with a median age 38.36 years; 13.34% (8 patients) with higher education, 40% (24 patients) with secondary education, and 46.66% (28 patients) with elementary education. All subjects were invited to match one randomly selected spoken text (in Romanian) defining one of the seven types of stools with one of the seven drawings from the original scale. This was performed twice for each subject, resulting in two pairs of question-answers. For re-test reliability a randomly selection of 10% of subjects were invited to repeat the procedure after 14 days.

The overall value for Cronbach's alpha was 0.892 for the first pair of questions and answers, respectively 0.953 for the second pair (ranges 0.844 - 1), indicating adequate test-re-test reliability and internal consistency for each subgroup [9].

The intraclass correlation coefficient (ICC) that ensures the reproducibility of a scale or questionnaire by measuring the consistency or homogeneity of measurements was 0.805 for the first pair, and 0.911 for the second pair question-answer, respectively. Excellent reliability [10, 11] with value ≥ 0.90 indicates small bias [12], supporting the reliability of the translated scale.

This study confirms that the Romanian version of the BSFS proposed by us is reliable and can be used to evaluate stool form and consistence.

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Scala Bristol a formei scaunului

<i>Tip 1</i>		Bucăți mari separate, asemănătoare cu nucile (greu de eliminat)
<i>Tip 2</i>		Cu formă de cârnat, dar constituit din bucăți (tare)
<i>Tip 3</i>		Asemănător unui cârnat, dar cu crăpături la (pe) suprafață
<i>Tip 4</i>		Asemănător unui cârnat sau unui șarpe, neted și moale
<i>Tip 5</i>		Fragmente moi cu margini bine definite (ușor de eliminat)
<i>Tip 6</i>		Bucăți pufoase cu margini neregulate, scaun moale
<i>Tip 7</i>		Apos, fără bucăți solide. COMPLET LICHID

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