Yücel Üstündağ
Covering the Cover Editor of this Issue

COVERING THE COVER

NSAID, antiaggregant and/or anticoagulant-related upper gastrointestinal bleeding: assessing the change in prophylaxis rate after a 10-year period

There is a lack of global awareness about using proton pump inhibitors (PPI) for prophylaxis of gastrointestinal (GI) side effects among patients using these drugs as well as physicians prescribing them. A primary GI side effect is bleeding due to erosion and/or ulcers in patients who frequently use NSAIDs, antiaggregant and/or anticoagulant drugs. This issue has been reported in a previous report from Turkey which showed that only 2% of patients who were prescribed such risky medicine for GI side effects were also simultaneously put on PPI prophylaxis. Other reports also confirmed low rates of PPI prophylaxis on such patients. In the present paper, the authors have investigated the recent trend for PPI prophylaxis in GI-bleeding patients, for which they recruited 96 patients with NSAID, antiaggregant and/or anticoagulant-related upper GI bleeding. They noted that only 21% of these cases were already undergoing PPI therapy for prophylaxis against GI side effects, and 86% of the cases who were at a high risk of NSAID-related GI bleeding were not undergoing PPI prophylaxis. Out of 44 patients who were treated by a cardiologist, 34 patients were not advised to take PPIs even though they were at a high risk of GI toxicity. Thus, this study draws our attention to the insufficient use of PPI prophylaxis in patients who are on NSAID, antiaggregant, and/or anticoagulant therapy, which may potentially create life-threatening GI side effects. See page 505.

Validity and reliability of (QoLRAD) questionnaire in patients with gastroesophageal reflux disease in a Turkish population

The main purpose of treating patients with gastroesophageal reflux disease (GERD) is to improve their quality of life. To assess this, the quality of life in reflux and dyspepsia (QoLRAD) questionnaire is the most common and practical in its usability. It has been translated by physicians worldwide into their respective languages to test the validity and reliability of QoLRAD in their countries. The present study aimed at investigating the validity and reliability of the Turkish version of this questionnaire in Turkish patients suffering from GERD. The authors assessed 142 patients in a tertiary referral center who presented with heartburn and regurgitation once a week or more and had an upper endoscopy and pathologic 24-hour ph/impedance monitorization consistent with GERD. After the QoLRAD was translated into Turkish by meticulous experts who were fluent in both English and Turkish, the patients (who were off proton pump inhibitor therapy for at least 10 days) were asked to fill up the socioeconomic data collection form, QoLRAD-TR, and short form (SF-36). The authors analyzed the Pearson Product Moment correlation between the QoLRAD-TR and reference form SF-36 (>0.6 was considered good). They investigated the internal consistency of QoLRAD-TR form using Cronbach's alpha coefficient method (> 0.7 was considered excellent). Additionally, the authors analyzed the questionnaire with regard to its consistency, by re-applying the QoLRAD-TR questionnaire in 31 patients 2 weeks after the first interview. By this method, they were able to measure the time invariance of the QoLRAD-TR results in line with the test-retest results. The overall Cronbach's alpha coefficient was found to be 0.97 and the intraclass correlation coefficient (ICC) was found to be between 0.97 and 0.99. The ICC values were higher than what has been reported by all the other studies on the QoLRAD questionnaire. The authors also noted that there was a positive correlation between all the subdomains of QoLRAD-TR and SF-36 questionnaire. The authors concluded that the QoLRAD-TR questionnaire was valid and reliable for Turkish patients to assess the the current status of GERD. Further, it would be very demonstrative to use this form for our patients with GERD on treatment with PPIs and/or after other more radical therapies, such as stretta, anti-reflux mucosotomy, and/or reflux surgery. See page 511.

Distribution of nucleotide variants in the DNA sequence of ERCC1 and XRCC1 genes in gastric cancer patients and their effects on the phenotype

Gastric cancer is one of the most common types of cancer, especially in Eastern Asia, and the second most common cause of cancer-related mortality worldwide. The pathogenesis of gastric cancer represents a classic example of gene-environment interactions. Genetic factors play an important role in gastric carcinogenesis due to aberrant gene expression that causes a malignant phenotype. The oncogenic activation of β-catenin and K-ras, amplification of the c-erbB2 and c-met genes, p53 and APC gene muta-

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tions, somatic mutations of E-cadherin, runt-related transcription factor 3 (RUNX3), and microsatellite instability (MSI) are associated with the pathogenesis of gastric cancer. In this issue of the Turkish Journal of Gastroenterology, the authors investigated the phenotypic relationship of polymorphism or mutation of nucleotide substitutions determined by DNA sequence analysis in the XRCC1 and ERCC1 genes belonging to BER and NER families of DNA repair genes in gastric cancer patients. In this prospective study, 50 patients with gastric cancer (study group) and 50 healthy males and females (control group) with no malignancy were enrolled. The phenotype findings (tumor size, tumor localization, tumor histopathologic type, and lymph node metastasis rate) were compared to the patient gender in gastric cancer patients and genotype distribution and allele frequency were detected in XRCC1 and ERCC1 gene. The results showed that mutations in the XRCC1 gene codons 194, 280, and 399 are not associated with patient's sex, age, tumor localization, tumor diameters, tumor histopathologic type, or lymph node metastasis. Besides this, no mutations were detected in any exons of ERCC1 gene in patients with gastric cancer and in the healthy subjects. According to this study, gastric cancer patients and healthy people in the Turkish population do not carry an ERCC1 gene mutation. Three mutations were detected in the XRCC1 gene but these mutations were not associated with gastric cancer. Recent studies showed conflicting results about the effect of these gene mutations in gastric cancers. Further investigations are needed into these gene mutations in patients with gastric cancer among different populations as well as in the Turkish population. This could give way to new insights into the treatment of gastric cancer, such as targeted therapy for special populations with a predilection for this deadly tumor. See page 517.

Diagnostic accuracy of glycoproteins in the assessment of liver fibrosis: A comparison between laminin, fibronectin and hyaluronic acid

The assessment of liver fibrosis by non-invasive methods is an important research subject in hepatology. During liver fibrogenesis, liver injury is characterized by the accumulation of fibrillar collagen and various extracellular matrix proteins, including glycoproteins such as laminin, fibronectin, and hyaluronic acid. Laminin and hyaluronic acid are synthesized by hepatic stellate cells and fibronectin is synthesized by Kuppfer cells, endothelial cells, and hepatocytes. These protiens have various important biological functions and are vital to the formation of the skeletal backbone of the collagen matrix. There have been various studies indicating that the serum levels of these glycoproteins can reflect the activity of liver fibrosis. In this meta-analysis, the authors analyzed the results of 11 studies investigating these glycoproteins in patients with chronic hepatitis B and C infection and non-alcoholic fatty liver disease (NAFLD). The serum laminin levels were found to increase dramatically in patients with cirrhosis and the cut-off point of 60 ng/ml had a sensitivity and specificity of 71% and 77% respectively in the assessment of significant fibrosis. It was also reported that laminin serum concentration at AUC 0.71 can distinguish significant liver fibrosis from mild fibrosis. This increase may be due to deteriorated or impaired liver endothelial cell functions owing to laminin degradation. One study in this meta-analysis also concluded that serum fibronectin can be useful in distinguishing patients with liver fibrosis from healthy individuals with a sensitivity and specificity of 75% and 82% at an AUC of 0.78. Another report defined a novel index termed as the fibronectin discriminant score (FDS), which showed good accuracy with AUC of 0.90 for the FDS cut-off value of 0.35 and AUC at 0.86 for an FDS cut-off of 0.55. ROC for laminin, fibronectin, and hyaluronic acid was found to be correlated with AUC of 0.89, 0.82, and 0.73 respectively. The results of this meta-analysis indicated that these glycoproteins can be helpful non-invasive indicators of the degree of liver fibrosis in patients with chronic hepatitis B and C infection and NAFLD. It seems to be possible to use these indicators as screening tools and to define a practical diagnostic index by combining three of them into one system. See page 524.

Assessing end-stage liver disease and pneumonia: An improved scoring model for critically ill cirrhotic patients with pneumonia.

Pneumonia is a common but serious infection, especially in patients with advanced stage liver cirrhosis with a mortality rate as high as 40%. In critically ill cirrhotic patients with pneumonia, the existing scoring systems are MELD, MELD-sodium, CURB65, and pneumonia severity index (PSI). Another risk index for cirrhotic patients with community-acquired pneumonia is named MELD-CAP. Indeed, CURB65 and PSI are not better than MELD at predicting mortality as the main determinant of death in these patients is usually the degree of liver failure. In this study, the

authors tried to create a new risk model (MELD-P) by combining the liver failure index (MELD) with the pneumonia severity parameters (SPO2/FIO2) to predict in-hospital and short-term (up to 21 days) mortality in critically ill patients in the intensive care unit suffering from cirrhosis and pneumonia. A total of 231 patients (stratified into training and validation cohorts) were included in this study. MELD-P score contained parameters like bilirubin, INR, use of vasopressin, and SPO2/FIO2 (R: 2.6x loge [bilirubin mg/dl] + 12.7x [INR]−9.7xloge SPO2/FIO2+13.1x [vasopressin use, 1 yes, 0 no]). After AUROC analysis in both cohorts, the authors concluded that MELD-P predicted the 21-day, 14-day, 7-day and in-hospital mortality much better than MELD, MELD-Na, PSI, and CURB65. Thus, the timely and accurate estimation of the prognosis of cirrhotic patients in the intensive care unit with developing pneumonia is a highly important issue. I believe that this new risk model for prognosis (MELD-P) can help our therapeutic approach in patients with advanced stage liver failure and pneumonia in intensive care settings. Nevertheless, I agree with the authors that large scale multicentric studies are needed to verify the success of MELD-P in other cohorts as well. See page 532.

Characteristics and early mortality in patients with hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in the world and yet, its prognosis remains poor. In the present single-center retrospective study, the authors scrutinized the risk factors for HCC-associated early death (within 6 months from the initial date of diagnosis of HCC). They enrolled 131 patients into the study and found that 43 deaths occurred between 2012 and 2017. Out of these 43, 21 patients died within the first 6 months from the date of initial diagnosis. Several demographic data (age, sex, etiology, laboratory values, hepatic reserve, performance status, TNM staging, BCLC level, and JSI) were analyzed. The type of treatment was also assessed (TACE, resection, RFA, infusion chemotherapy, molecular targeted therapies, and best supportive care (BSC)). Univariate analysis showed that the early-death group included more patients with older age and with lower performance status. This group also included more patients with tumor nodules greater than 3 cm than non-early-death group. The early-death patients also had the worst Child-Pugh scores, advanced TMN/BCLC stages, highest JIS scores, and it was found that the least number of them had undergone aggressive treatment modalities mentioned above. Logistic regression analysis revealed that a large maximum nodule diameter (>3 cm), high JIS score, and absence of initial aggressive treatments were independent predictive factors for early mortality in patients with HCC. The early-death group was reported to have undergone less aggressive treatments than recommended according to BCLC stage, while nearly 63% of the non-early-death patients underwent similar or more aggressive treatments than recommended by relevant BCLC stage. Aggressive treatments were shown to improve the prognosis of patients with advanced HCC (BCLC -C/D, maximum tumor diameter >3 cm, and a JIS score of 4 or 5). In this group, patients who received aggressive treatments in place of than BSC were found to avoid an early death from HCC. A correlation analysis revealed that JIS was found to be the best parameter to correlate with early mortality. Thus, the authors concluded that even in patients with advanced stages of HCC, aggressive treatment approaches appear to help these patients stay alive within a 6-month period after diagnosis. Nevertheless, the authors did not mention the causes of death in the early or late mortality group which was a primary limitation of this study. Another limitation was that there was no investigaton by the authors as to why the early-death group did not receive optimal treatment according to the BCLC staging. See page 541.

Assessing the diagnostic value of blue laser imaging combined with magnifying endoscopy for precancerous and early gastric lesions

Blue laser imaging (BLI) is a relatively new imaging modality with two modes of laser application. One is the contrast mode, which uses a 410 nm laser and visualizes vascular microarchitecture and similar narrow band imaging, while the other bright mode uses an excitatory white light 450nm laser that visualizes mucosal microvascular and microtubular structures. There are few studies in the literature that have investigated the performance of BLI in diagnosing early gastric cancers compared to white light endoscopy, which often misses early gastric neoplastic pathologies. In the present paper, the authors scrutinized the diagnostic accuracy of BLI technique combined with magnifying endoscopy in 235 patients having 249 gastric lesions. The authors classified the lesions into regular, irregular and absent based on their microvascular and microtubular morphology. They also noted the boundary between the lesion and surrounding

mucosa and demarcated a dividing line if this boundary was clearly seen on BLI investigation. Pathologic diagnosis was made according to the revised Vienna criteria for gastric cancer and/or high-grade dysplasia diagnosis. They ended up with a pathologic diagnosis of chronic gastritis in 149 patients, intestinal metaplasia in 67 patients, low-grade dysplasia in eight patients, and high-grade dysplasia/cancer in 25 patients. BLI contrast mode showed irregular or absent microvascular morphology in 96% of cancerous lesions but was regular in 95% of noncancerous lesions. Absent or irregular microtubule morphology was seen in 96% of cancerous lesions, but only in 4.4%of noncancerous lesions. A clear demarcation line was seen in 92% of cancerous lesions, but it was absent in 99.1% of noncancerous lesions. BLI bright mode also showed similar numbers of abnormal microvascular and microtubular anatomy in cancerous and noncancerous lesions, but with a higher rate of occurrence of the demarcation line between the cancerous and noncancerous lesions (100%). They also noted that the pathologic diagnosis was found to correlate with BLI combined with magnified endoscopy findings rather than white light endoscopy imaging combined with the magnification-based diagnosis. For early diagnosis of gastric cancerous lesions, white light endoscopy had a sensitivity of less than 80% and BLI combined with magnifying endoscopy improves this number to more than 90% with a kappa value of over 0.8 for endoscopic and pathologic diagnosis. This study clearly showed the superiority of BLI over white light endoscopy in the early diagnosis of gastric cancerous lesions, alone or in combination with magnifying endoscopy. See page 549.

Protective effects of alendronate in Trinitron X-induced hyperlipidemia in rats

Alendronate is an inhibitor of osteoclast-mediated bone resorption. This drug also acts on the mevalonate pathway and inhibits farnesyl pyrophosphatase, which is the key enzyme in cholesterol synthesis. This study investigated the dual therapeutic effects of alendronate on an animal model of hyperlipidemia induced by Triton X 100 in rats. Triton X 100-treated rats showed significantly increased serum TC, LDL-C, VLDL-c, TGs, AST, ALT, and decreased HDL-C levels. In this rat model of acute hyperlipidemia, alendronate (1.5 mg/kg and 3 mg/kg) produced a dose-dependent reduction in serum levels of total cholesterol (TC), VLDL-C, TG, TC/HDL-C ratio, liver enzymes including ALT, AST, thiobarbituric acid reactive substances, and superoxide dismutase (SOD) activity, but did not provide significant decrease in serum LDL-C levels. Liver histopathology indicated minute changes in peribiliary inflammatory cell infiltrates, lower capsular thickening, and normal arrangement of hepatocytes around the portal and central vein. This study confirmed that alendronate has both hepatoprotective and anti-hyperlipidemic effects, which can be a potential reason to use this drug to treat patients with metabolic syndrome and osteoporosis. It is also obvious that we need further studies to investigate the mechanism of its hepatoprotective effects. See page 557.