
COVERING THE COVER

Toll-like receptor 2 and 4 polymorphisms associated with *Helicobacter pylori* susceptibility and gastric cancer

Gastric cancer (GC) is the leading cause of deaths due to cancer worldwide and is the fourth most common type of cancer in men and the sixth most common in women in Turkey. Although *Helicobacter pylori* infection plays a crucial role in the development of gastric mucosal atrophy and GC, the pathogenesis of GC is multifactorial and involves combined effects of bacterial, host, and environmental factors. Toll-like receptors (TLRs) are a class of innate immune-recognition receptors that play a central role in recognizing molecular patterns associated with microbial pathogens and inducing antimicrobial immune responses. Recent studies have reported associations between TLR polymorphisms and the risk of development of GC in different populations.

In this issue of the Turkish Journal of Gastroenterology, Tongtawee et al investigated TLR polymorphisms (TLR2 rs3804099 and rs3804100 and TLR4 rs10759932) in 400 Thai patients and evaluate the association among genotypes and the risk of development of gastric lesion and susceptibility to *H. pylori*. They found that TLR4 rs10759932, C/C homozygous genotype was associated with an increased risk of premalignant/malignant (atrophy, intestinal metaplasia, and GC) conditions (OR = 2.48, 95% CI = 1.96–4.62, $p = 0.015$). The recessive model of TLR4 rs10759932 was associated with a decreased risk of susceptibility to *H. pylori* and an increased risk of non-malignant condition (chronic gastritis).

This study demonstrates that TLR polymorphisms are significantly associated with the risk of gastric premalignant/malignant conditions as well as susceptibility to *H. pylori*. Further validation of these findings in different populations will help to explain why some parts of *H. pylori*-infected individuals develop GC and may provide novel insights into developing new therapeutic strategies and improve the primary and secondary prevention of *H. pylori*-related GC in high-risk populations. See page 15.

Predictors of poor outcomes in 488 patients with herb-induced liver injury

The use of complementary and alternative medical therapies including herbal and dietary supplements has continued to increase dramatically worldwide. Many people consider "natural" herbal products to be completely free of undesirable side effects. Approximately

55 million adults reported the use of these products in the United States. However, there is now a growing worldwide concern about severe liver injury due to these medicines. It has been estimated that approximately 15% of drug-induced liver injuries are caused by herbs. Prognostic scores to early predict the clinical outcome for herb-induced liver injury (HILI) are poor or rudimentary.

In this issue of the Turkish Journal of Gastroenterology, Zhu et al. studied 488 (0.8%) patients with a diagnosis of HILI among 61,516 patients hospitalized due to liver injury to identify the predictors of poor outcomes (chronicity, liver transplantation, or death). The mean age of the patients was 45 years, and 70% of the patients were female. HILI was diagnosed according to the Chinese Society of Hepatology guidelines and Roussel Uclaf Causality Assessment Method score. The cases were divided into three groups: (1) recovered after herb(s) discontinuation, (2) chronic HILI (sustained abnormalities at 6 months after the HILI onset), and (3) fatal HILI (dead or liver transplantation). HILI was classified as hepatocellular (86.1%), cholestatic (6.3%), or mixed pattern (7.6%). The Model for End-Stage Liver Disease (MELD) score and positivity for Hy's law were also determined. After discontinuation of herb(s), of the patients, 82% healed, 14% developed chronic HILI, 0.2% underwent liver transplantation, and 4% died. The MELD score was found to be superior to Hy's law in predicting fatal outcome. The authors have formulated a risk score for predicting chronicity using variables (latency, course of peak alanine aminotransferase decreasing $\geq 50\%$ after herbal intake discontinuation, peak triglyceride value, and platelet count at the liver injury onset) determined by multivariate logistic regression to be significantly related to chronic HILI. This prognostic model yielded more accurate predictions of chronicity than MELD and Hy's law.

Although the authors reports a low frequency (0.8%) of HILI among patients hospitalized due to liver injury, it is worth emphasizing that many patients do not report the use of herbal products to their clinicians; therefore, HILI may be missed. The present study closes a significant gap in the literature by investigating the predictors of poor outcomes in HILI cases. Validation of HILI chronicity model suggested in the current study in additional populations would help to clarify the value of this model. See page 47.

Lamivudine's efficacy and safety in preventing mother-to-child transmission of hepatitis B: A meta-analysis study

The risk of vertical transmission of hepatitis B virus (HBV) from chronically infected hepatitis B surface antigen (HBsAg)-positive mothers to their newborns (mother-to-child transmission (MTCT)) has been reported to be as high as 90% without the use of active and passive immunization. Fortunately, this risk appears to be reduced with the introduction of universal maternal HBV screening, vaccination of all newborns, and the use of hepatitis B immune globulin (HBIG) for newborns of HBsAg-positive mothers. Although the combination of passive and active immunization in these newborns reduces vertical transmission of HBV, this immunoprophylaxis cannot completely eradicate MTCT. The administration of antiviral agents to pregnant women with high viral loads has been shown to be safe and effective in reducing MTCT of HBV in combination with immunoprophylaxis.

In this issue of the Turkish Journal of Gastroenterology, Khalighinejad et al. conducted a meta-analysis of 25 studies (up to January 2016) that enrolled 2667 HBV-infected pregnant women to evaluate the efficacy and safety of lamivudine during pregnancy in the prevention of MTCT. The case group (1394 women) received lamivudine, and the control group received HBIG or no treatment. The analysis revealed that the use of lamivudine therapy compared with the control reduced the likelihood of MTCT as defined by newborn HBsAg seropositivity (relative risk (RR)=2.07, 95% CI=1.73-2.47), infant HBsAg seropositivity (RR=16.97, 95% CI=8.36-34.45), newborn HBV DNA positivity (RR=9.68, 95% CI=5.66-16.56), and infant HBV DNA positivity (RR=10.77, 95% CI=4.92-23.58) (all p value <0.0001). There was no statistically significant difference when comparing lamivudine versus control for fetal and maternal adverse outcomes. Lamivudine therapy could induce a >6 log₁₀ IU/mL (95% CI=-7.836 to -5.552) decline in maternal HBV DNA.

This meta-analysis affirms the effectiveness of lamivudine in the prevention of vertical transmission of HBV infection. The current guidelines (American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL)) recommend antiviral therapy for pregnant women with serum HBV DNA >200,000 IU/mL (or >106 copies/mL) or with advanced fibrosis or cirrhosis. Which antiviral drug should we use? Only tenofovir and telbivudine are pregnancy category B drugs. The others including lamivudine are pregnancy category C drugs. Accordingly, both guidelines (AASLD and EASL) recommend

tenofovir as a preferred drug owing to its antiviral potency and concerns for resistance with other antiviral agents. The present meta-analysis confirms that lamivudine is a reliable option to prevent MTCT of HBV in circumstances that we cannot use tenofovir (i.e., renal impairment, severe headache, and clinically significant creatine kinase elevations). See page 66.

Low-molecular weight heparin treatment of acute, moderate, and severe pancreatitis: A randomized, controlled, open-label study

A variety of evidence shows that activated systemic inflammatory cascades and microcirculatory disturbances are the key factors in the pathogenesis of severe acute pancreatitis (AP) and play a major role in the development of multiorgan failure. A few studies on humans and animals have shown that low-molecular weight heparin (LMWH) can reduce the release of cytokines and inflammatory mediators, resulting in an improvement of the microcirculation of the pancreas, and clinically, it can mitigate the complications of AP.

In this issue of the Turkish Journal of Gastroenterology, Tozlu et al. conducted a randomized, controlled, open-label study to determine the effect of LMWH (enoxaparin sodium) on the prevention of pancreatic necrosis (PN) in patients with moderately severe and severe AP according to the revised Atlanta criteria. According to a power analysis, the authors enrolled 100 patients into the study and randomized them to receive either standard care (SC, n=50) or SC plus LMWH (n=50). The mean age of the patients was 52 years. The male-to-female ratio was 46/54. The main etiology was biliary (55%), and the majority of patients (97%) had moderate severity. LMWH was administered at 1 mg/kg subcutaneously twice a day between days 1 and 7. The primary outcome measure was the development of PN on repeated contrast-enhanced CT on day 7. The secondary outcome measures were time to tolerate oral intake and development of local and systemic complications. Over a period of 16 months of follow-up, PN developed more frequently in the SC group than in the LMWH group (6.1% vs. 22.9%, p<0.05). In addition, local (14% vs. 34%) and systemic complications (36% vs. 74%) were found to be significantly lower in the LMWH group (p<0.05). Hemorrhagic complication was not detected. Five patients died, and all were in the SC group.

These results demonstrate that the addition of LMWH in the SC of moderately severe and severe AP is a safe and effective method in the prevention of PN and local and systemic complications. See page 81.