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INTERLEUKIN-22 THERAPY FOR USE IN NON-ALCOHOLIC FATTY LIVER DISEASE

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We discovered that the cytokine interleukin-22 (IL-22) is an efficient natural inhibitor of cellular stress and improved insulin quality in pancreatic beta-cells in preclinical models of Type 2 diabetes. Importantly, IL-22 completely restored glucose tolerance, suppressed fasting hyperinsulinaemia/hyperproinsulinaemia, and restored insulin sensitivity in obese animals. Treatment of obese animals with IL-22 also showed significant improvements in circulating triglycerides, liver function (AST:ALT ratio) and a reduction in hepatic lipid accumulation. IL-22 has also been shown to be protective in other models of liver disease including alcoholic hepatitis, acute-on-chronic liver failure, hepatic fibrosis and paracetamol induced liver injury, and there are 3 versions of IL-22 based therapeutics in clinical trials for such pathologies. Interestingly, the IL-22 receptor, IL-22Ra1 is highly expressed in the pancreas and liver. Our study aimed to define the role of endogenous IL-22 in the liver and pancreas to provide additional support for IL-22 therapy in non-alcoholic fatty liver disease (NAFLD).

To achieve this, we generated tissue specific IL-22Ra1 knockout mice lacking the receptor in pancreatic beta-cells (IL-22Ra1b-cell -/-) and hepatocytes (IL-22Ra1Hep -/-). We then challenged them with a high fat diet, and measured their glycaemic control, hepatic lipid accumulation, and hepatic markers of cellular stress, lipid, and glucose metabolism. Through this, we found that IL-22Ra1b-cell -/- animals had increased hepatic markers of inflammation and cellular stress. Interestingly, we also observed this phenomenon in IL-22Ra1b-cell -/- mice. Additionally, IL-22Ra1b-cell -/- animals also had defective glycaemic control and insulin secretion compared to littermate control animals, which worsened on a high-fat diet. We also found that whilst female animals did not gain as much weight as male animals on a high-fat diet, female IL-22Ra1b-cell -/- mice had a worsened phenotype compared to males.

In conclusion, we confirmed the role of endogenous IL-22 in maintaining insulin quality control and healthy hepatic function. We also discovered a novel role for endogenous IL-22 in the pancreatic-beta cell-liver axis and demonstrated the importance of targeting IL-22 to both pancreatic beta-cells and hepatocytes to treat NAFLD.

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STATINS PROTECT AGAINST THE RISK OF ACUTE CHOLANGITIS IN PATIENTS WITH PRIMARY SCLerosING CHOLANGITIS

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Background and Aims: Primary sclerosing cholangitis (PSC) is a cholestatic biliary disease and patients with PSC are at increased risk for developing acute cholangitis. Alterations in bile acid homeostasis is a hallmark of cholestatic disease, many patients with PSC are prescribed medications that alter bile acid metabolism, including statins for co-morbid cardiovascular disease, and bile acid sequestrants for itching. However, the epidemiological risks of these medication in PSC have not been studied. Methods: We conducted a multicenter, retrospective cohort study using data from 294 patients at Stanford Medical Center, Baylor University Medical Center, and Santa Clara Valley Medical Center, a county healthcare system. Patient demographics, medications, PSC disease severity, and IBD disease status were extracted. Using stepwise variable-selection process, demographic and covariate predictors were included in the multivariate logistic regression model assessing risk factors for cholangitis. Time-to-event analysis was performed to evaluate the impact of medications that affect bile acid metabolism on the development of cholangitis Results: Thirty percent of patients had at least one episode of acute cholangitis (n=87). Statin therapy was associated with decreased odds of acute cholangitis (OR 0.22, 95% CI 0.07-0.62), but bile acid sequestrant use was associated with increased odds of acute cholangitis (OR 4.91, 95% CI 2.05-12.37). Statin therapy was associated with increased time-to-cholangitis, with an incidence of 8.6% at 36 months compared to 51.6% for patients not on statin therapy. Conclusions: Our observations suggest that medications that alter bile acid metabolism differentially modify the odds of acute cholangitis. Statin therapy was shown to be potentially protective against the development of acute cholangitis while bile acid sequestrant therapy was associated with increased odds of cholangitis.

Figure 1. Time to cholangitis on statin and bile acid sequestrant therapy
ASSESSMENT AND VALIDATION OF THE TREAT-B SCORE FOR CHRONIC HEPATITIS B VIRUS TREATMENT ELIGIBILITY

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Introduction: Hepatitis B virus (HBV) DNA is a key marker for considering antiviral therapy eligibility. However, the assay is not widely available, particularly in low- and middle-income countries. TREAT-B, a new simple and low-cost score was developed for determining treatment eligibility in resource-limited countries. A TREAT-B score ≥ 2 has been proposed as the treatment threshold in the African cohort (Shimakawa Y et al). This study aimed to assess and validate the performance of the TREAT-B score for HBV treatment eligibility. Method: We conducted a retrospective analysis of consecutive treatment-naive chronic HBV mono-infected patients with complete data who visited the liver clinic at Chulalongkorn University Hospital, Bangkok, Thailand, from January 2015 to February 2021. The American Association for the Study of Liver Diseases (AASLD) 2018 guideline was considered as the reference standard. The performance of the TREAT-B score and simplified World Health Organization (WHO) criteria for patient selection for antiviral therapy were evaluated. TREAT-B was obtained by adding HBVAg status (negative = 0 points, positive = 1 point) and ALT ≥ 20 U/L (0 points, 20-39 U/L 1 point, 40-79 U/L 2 points, ≥ 80 U/L 3 points). Result: Overall, 639 patients were analyzed, 320 (50.1%) were women, and the mean age was 46.9 ± 12.5 years. The mean ALT was 56.1 ± 141.1 U/L, 371 (24.1%) were HBcAg positive, 31 (4.9%) were carrier, and 307 (7.8%) patients were eligible for treatment according to the AASLD 2018 guideline, 451 (70.6%) based on the TREAT-B score, and 376 (58.8%) based on the simplified WHO criteria. Performance of the TREAT-B and simplified WHO criteria to select patients eligible for antiviral therapy compared to the reference was shown in Table 1. The upper receiver operating characteristics curve (AUROC) of the TREAT-B score (0.85, 95% CI 0.82-0.88) was better than the simplified WHO criteria (0.63, 95% CI 0.59-0.68, p < 0.001). The sensitivity, specificity, and AUROC of the TREAT-B were 95.9%, 46.0%, and 0.66 (95% CI 0.62-0.80, respectively. Therefore, using the cut-off of ≥ 2, 59.4% of patients receiving antiviral would not have been needed. Applying the TREAT-B score ≥ 3 improved the specificity (87.4%) and AUROC (0.80, 95% CI 0.76-0.84), but reduced sensitivity (71.4%) for selecting patients for HBV therapy. Conclusion: In resource-constrained countries where HBV DNA is unavailable, the TREAT-B score is a better alternative than the simplified WHO criteria for indicating treatment eligibility. Using the TREAT-B score ≥ 3 has high accuracy and may minimize the number of patients unnecessarily treated lifelong in the Asian HBV-monoinfected patients.